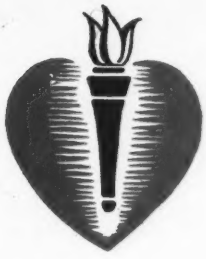
NOVEMBER 1956
VOL. XIV NO. 5

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION



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1. Binder, M. J., et al.: **Am. Jour. Med.**, 18:62, Apr., 1955. 2. Sampson, J. J., and Zipser, Albert: **Circulation**, 9:38, Jan., 1954. 3. Nichol, E. S., in Conn, H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. 4. Jamison, W. L., et al.: **Jour. Am. Geriat. Soc.**, 3:521, Aug., 1955. 5. Gilchrist, A. Rae: **Brit. Med. Jour.**, 2:351, Aug. 16, 1952.

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Editorial

Cerebral Vascular Diseases: An Area of Opportunity

CEREBRAL vascular diseases have been described[1] as one of the most neglected areas of all medicine. Patients with cerebral vascular diseases are perhaps the most neglected of all patients—neglected by physicians, family, friends, society, even themselves.

During recent years, however, an awareness has grown that cerebral vascular diseases represent not merely a very great burden, but also a great potential for progress. Signal evidence of the recognition of this underdeveloped area of clinical medicine and public health was the first national conference on cerebral vascular diseases held under the auspices of the American Heart Association in 1954. The need for action in this broad field of human disease and related human misery began to be delineated at the conference and undoubtedly will be further crystallized in forthcoming meetings. Thus the need to do something constructive is becoming more and more widely recognized because, with the passage of time in our aging population, the burden grows even more overwhelming. Cerebral vascular diseases sooner or later will affect every individual in the population who lives long enough. For this reason, it is perhaps the most all-inclusive single health problem that can be named.

Yet, thus far, all the resources of research, education, and community service that should be brought to bear upon the problem have not been marshaled.

True, many resources are in one way or another attacking it. Although existing knowledge is inadequate to prevent a major proportion of the many thousands of cerebral accidents that occur each year, existing knowledge is adequate to correct much of the disability that results from many of these catastrophes, through ever-improving technics of rehabilitation. Unfortunately, however, at present only a small fraction of the victims of cerebral vascular accidents receive full benefits of current knowledge. It has been demonstrated that the field of rehabilitation, particularly because of its progress in the last few years, offers resources that can do a great deal for many of the victims of strokes and of other aspects of cerebral vascular diseases. The actual provision of rehabilitation technics of almost all kinds, however, has been done more upon a "demonstration" basis than otherwise.

Professional and public education, of course, is involved in rehabilitation procedures themselves and in the care of individuals suffering from cerebral vascular diseases. Here, too, there is progress, but again, as a demonstration rather than upon a wide basis. There is very little available in the way of educational materials for either professional or public audiences. For example, such things as booklets for the physician to use with patients or their families are nonexistent, or almost so.

Research is a third area of opportunity for progress against cerebral vascular diseases. Research has made and is making great progress. The expanded and expanding programs of research, both in basic fields and in those specifically oriented toward chronic illnesses, cannot but result in further knowledge of great value in helping to solve problems of the cerebral vascular diseases. Yet it cannot be

claimed that a comprehensive research program has been mounted against them, and there are undoubted gaps and lacks.

The importance of the research need does not have to be compared to the importance of the needs in the application of knowledge. Research is, of course, the paramount need, and one that pervades the spectrum of the problem of cerebral vascular diseases. Really adequate solutions will come only with intensified research efforts in the medical, biologic, and allied sciences. Significant progress and the greatest ultimate benefits can be expected only through a concerted attack along many research fronts. This does not mean, however, abandonment of endeavors in widening application of knowledge, through better treatment and management of patients, through such preventive measures as are now available, through rehabilitation technics, and through professional and public education. These efforts ought also to be increased, and, with concurrent evaluative studies, they can be improved as they are more extensively applied.

The sum of the need, then, is the sum of the needs for action in research and education, and in community and individual services against the cerebral vascular diseases. The sum of the action that can be taken is represented by all the resources that can be brought to bear and all the efforts now being made. It is suggested that a point in time has been reached when resources and efforts can be logically focused upon this group of diseases that cause some 170,000 deaths each year and an amount of disability and suffering unknown in its precise extent, but surely vast.

Here is opportunity that will cry more loudly for greater recognition and greater action as tomorrow succeeds today. Many ears have already heard this cry; their number will increase. The first need is to translate the interest, already manifest on the part of many people in many fields, into implementation of a cooperative, multifaceted program. The interests of research and medicine and public health have a common bond in this very broad problem. Together, they can determine what each can contribute to a unified nationwide effort. Together, they can mobilize resources and efforts.

Because of their natural concern with diseases of the circulation and heart, interests in the cardiovascular field, where splendid partnerships exist between private and public organizations, can help bring about the kind of marshaling for action that is needed. A large-scale nationwide attack on cerebral vascular diseases, an integrated endeavor on the part of many people and agencies, would be particularly timely now. It would be likely to receive widest private and public support, by both voluntary and governmental organizations and by the general public.

The job needs to be done. It is not now being done. Now is the time to start. To seize the opportunity that lies in the area of cerebral vascular diseases, all that is required to start is the meeting of informed, determined, and inspired minds.

JAMES WATT

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The Effects of External Electric Currents on the Heart

Control of Cardiac Rhythm and Induction and Termination of Cardiac Arrhythmias

By Paul M. Zoll, M.D., Milton H. Paul, M.D., Arthur J. Linenthal, M.D., Leona R. Norman, M.D., and William Gibson, M.D.

Clinically, application of electric currents to the heart has been limited to defibrillation in the operating room when the heart is exposed. In this paper technics are described for the external application of stimulating and countershock currents. They have been used successfully in man to terminate ventricular standstill from any cause and to stop ventricular tachycardia or fibrillation. For experimental purposes an additional technic has been developed for producing various cardiac arrhythmias by rapid external stimulation of the heart.

THREE types of cardiac effects have long been known to result from the direct application of electric currents to the exposed heart: (1) stimulation of ectopic beats, (2) induction of arrhythmias, and (3) termination of arrhythmias. These procedures have been limited in experimental and clinical use because of the necessity of opening the chest. In this paper, technics are described whereby the same cardiac effects can be obtained when the currents are applied externally.

1. Single or repetitive electric stimuli applied directly to the heart are known to produce single ectopic beats or to assume control of cardiac rhythm. We have shown that electric stimulation applied externally across the unopened chest in man also produces effective cardiac beats and constitutes a valuable means of cardiac resuscitation from ventricular standstill.[1-5] Evidence is presented here that the external electric stimulator acts as an intrinsic cardiac pacemaker.

2. Repetitive electric stimuli have also been applied directly to the exposed heart to produce supraventricular and ventricular arrhythmias for experimental purposes.[6-8] We are presenting here a new technic of inducing these arrhythmias by electric stimulation of the heart across the unopened chest in the experimental animal with very rapid, monophasic impulses. This method of producing arrhythmias may prove valuable for physiologic and pharmacologic studies.

3. Electric countershock across the exposed heart has become the accepted therapy for ventricular fibrillation.[9, 10] In the experimental animal, ventricular fibrillation has also been terminated by external application of electric countershock across the unopened chest.[11-15] In this report we also show that countershock electric current of the same type that has long been used in open-chest defibrillation will, when applied across the unopened chest, instantaneously terminate atrial, nodal, and ventricular tachycardia as well as atrial and ventricular fibrillation. This technic of external countershock has been applied successfully for the first time to resuscitate a patient from ventricular fibrillation.

Methods

Studies on control of the cardiac rhythm by an external electric cardiac pacemaker and on external countershock defibrillation were performed primarily on 22 normal, adult mongrel dogs.

The data concerning the induction and termination of supraventricular and ventricular tachycardia

From the Medical Research Department of the Yasgains Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

This investigation was aided by research grants from the National Heart Institute, U.S. Public Health Service (H-1455 and H-1028), and from the Massachusetts Heart Association.

	STIMULATION	COUNTERSHOCK
Shape		
Duration	0.003 second	0.15 second
Intensity	25-100 volts .05-.2 ampere	180-720 volts
Electrode Diameter	3 cm.	7.5 cm.

FIG. 1. Optimum electric features for external cardiac stimulation and countershock.

were obtained in these dogs, in 5 normal domestic pigs (4 to 8 weeks of age and weighing 15 to 30 pounds), and mainly in 14 pigs previously subjected to ligation of the terminal portion of the left circumflex coronary artery. All pigs survived this ligation and were fully active within 24 hours. Postmortem examination showed small areas of myocardial infarction and significant interarterial coronary anastomoses.[16]

We have also observed the effects of external electric stimulation in over 70 patients and of external countershock in 5 patients to whom these currents were applied for therapeutic purposes.

Figure 1 shows the optimum characteristics of the 2 forms of electric current that were used for external stimulation and countershock of the heart.

Stimulating (Pacemaking) Current. A modified clinical cardiac pacemaker* with an extended range of rates of stimulation provided monophasic, rounded impulses of 3 msec. duration. The low internal impedance of the instrument (approximately 50 ohms) permitted adequate power output even across low body resistances. The stimuli were applied at rates of 60 to 1200/min. across external or esophageal electrodes. In the animals, surface electrodes (3 cm. in diameter, of brass with satin-nickel plating, and covered with conductive paste) or subcutaneous needle electrodes were placed on the right and left anterolateral chest walls in the cardiac area; at times a surface electrode was paired with an esophageal wire electrode at atrial or ventricular levels. In man, 2 surface electrodes were placed a few inches apart near the cardiac apex.

Countershock (Defibrillating) Current. Alternating current (60 cycle, 0.15 second, 180 to 720 volts) was applied across the unopened chest with large electrodes.* A special 6:1 isolation step-up transformer and a variable autotransformer* were used to convert the 120-volt line current to 0 to 720 volts. The duration of the countershock was fixed by a suitable condenser in a relay circuit similar to that described by MacKay, Mooslin, and Leeds.[17] The step-up transformer and the power-relay contacts were designed to carry approximately 12,000 watts (5 amperes at 720 volts) for 0.15 sec., repeated at intervals of 1 sec. In the animals, the countershock electrodes (10 by 15 cm. tin plates) were covered with electrode paste and applied firmly to the anterolateral chest walls in the cardiac area with a rubber strap to insure optimum electric contact. More recently, in man, in order to provide more rapid and convenient application of the countershock, copper electrodes, 7.5 cm. in diameter, mounted on heavily insulated handles, were held firmly in place on the chest wall, one to the left of the lower end of the sternum and the other lateral to the apex. Care was taken not to touch the electrodes or the animal's or patient's body during application of the high voltages.

The electrocardiographic response to external electric stimulation was monitored in all experiments with an oscilloscope† and recorded on a multichannel direct-writing electrocardiograph with paper speeds of 25 to 100 mm./sec.‡ Lead aV_F was used. An input-limiting preamplifier‡ and the "Instomatic switch" of the electrocardiograph, which shortens the time constant of the amplifier, were used at times during application of the large countershock currents to prevent wide swings of the electrocardiographic baseline and damage to the stylus.

In several experiments blood pressure tracings were recorded from the carotid artery or aorta with an electric pressure transducer.

CONTROL OF CARDIAC RHYTHM BY ELECTRIC STIMULATION

In the experimental animal and in man the electric stimulator acts as an externally controlled cardiac pacemaker, producing effective beats. The cardiac response to electric stimuli depends upon their frequency, intensity, and timing in the cardiac cycle. A stimulus above threshold in intensity that arrives in the responsive phase of the cardiac cycle produces an ectopic beat, either supraventricular or

* The cardiac pacemaker and external defibrillator are manufactured by the Electrodyne Company, Norwood, Mass.

* Variac V20, manufactured by General Radio Co., Cambridge, Mass.

† Cathode-ray oscillograph, type 304-A, manufactured by Allen B. DuMont Laboratories, Inc., Clifton, N. J.

‡ Manufactured by the Sanborn Company, Cambridge, Mass.

ventricular in origin (fig. 2). The threshold for effective cardiac stimulation ranged from 45 to 60 volts in the pig, 40 to 100 volts in the dog, and 20 to 100 volts (50 to 200 milliamperes) in man.

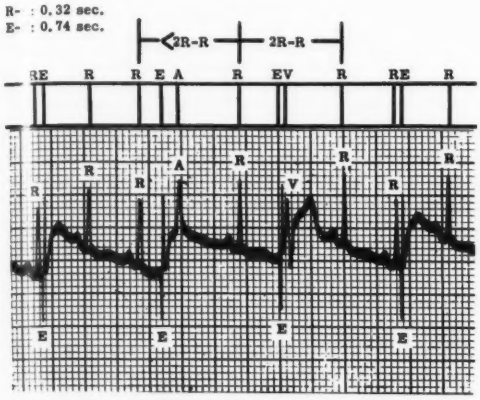

FIG. 2. External electric stimulation (dog). The first and last electric stimuli, E, are ineffective, since they fall in the refractory phase after the normal ventricular beat, R. The second and third stimuli fall in the responsive phase and evoke cardiac responses A and V: A, from a supraventricular focus, discharges the intrinsic sinoatrial pacemaker; the time between the preceding and succeeding R waves is less than 2 normal R-R intervals. V, from a ventricular focus, does not interrupt the sinoatrial rhythm; the time between the preceding and the succeeding R waves equals 2 normal R-R intervals.

With rates of stimulation slower than the intrinsic cardiac rhythm, intermittent ectopic beats are produced whenever the stimulus falls in a responsive phase of the cardiac cycle. The external electric pacemaker competes with the intrinsic cardiac pacemaker and all the phenomena of parasystole may appear (fig. 3).

At rates faster than the intrinsic pacemaker, the electric stimuli produce a regular, externally paced rhythm and mask the intrinsic cardiac activity (fig. 4). At frequencies of stimulation between 500 and 600/min. in the normal dog, the heart no longer responds to every stimulus and the externally paced rhythm becomes irregular; cessation of such rapid stimulation is usually followed by return of the intrinsic normal sinus rhythm.

In the normal pig regular 1:1 responses to the electric stimuli were recorded electrocardiographically at rates as high as 1000/min. (fig. 5). Simultaneous aortic pressure tracings showed small mechanical pulses synchronous with each electric cardiac response up to frequencies of 500/min. (fig. 5*B*).

With stimulation at 1000/min. (fig. 5*C*), pulse waves were not discernible, presumably because of insignificant stroke volumes. This absence of pulse waves confirmed the effectiveness of all the stimuli by indicating the suppression of the slower intrinsic pacemaker. The 1:1 electrocardiographic responses to the rapid

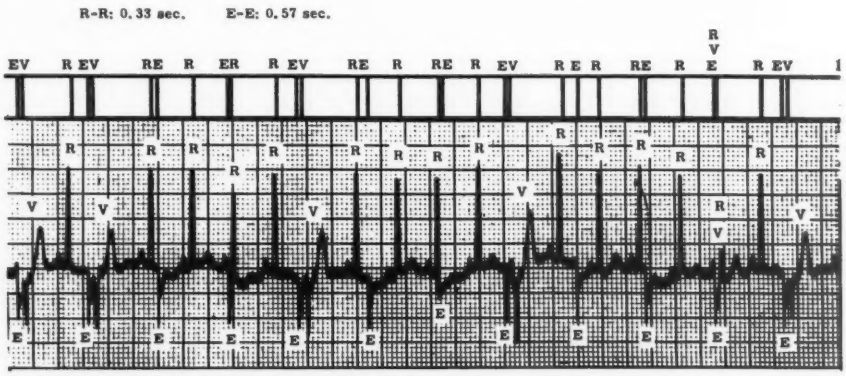

FIG. 3. Competition between the intrinsic sinoatrial and the external electric pacemakers (dog). When the stimuli, E, fall in the responsive phase of the cardiac cycle, they produce ectopic ventricular beats, V. The criteria for parasystole are fulfilled: (1) each V-V interval is a whole multiple of a constant interval, E-E; (2) the R-V interval is variable; and (3) a fusion beat, $\frac{R}{V}$, is present.

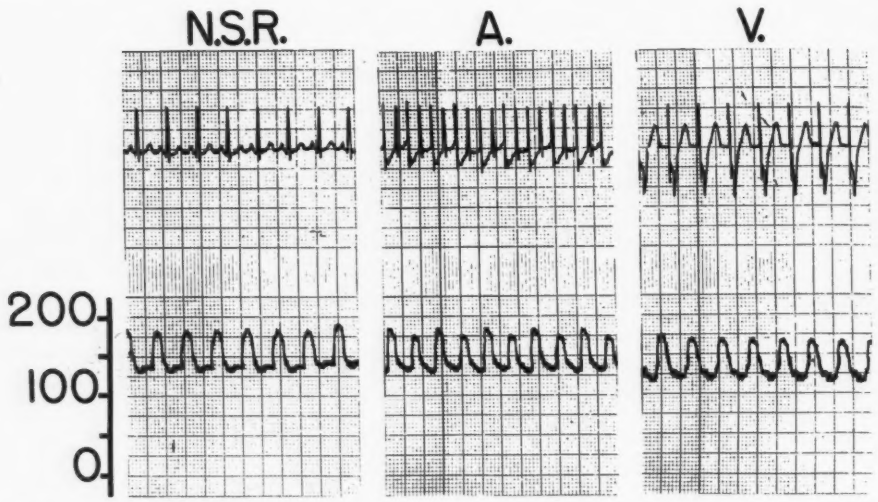

FIG. 4. Control of cardiac rhythm by supraventricular or ventricular stimulation (dog). The electric pacemaker, at a rate faster than the normal sinoatrial rhythm, N.S.R., produces a regular supraventricular, A, or ventricular, V, rhythm with comparable blood pressures. In this and subsequent figures the blood pressures are recorded in mm. Hg.

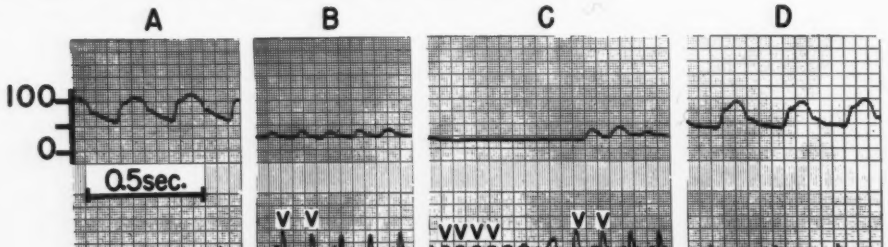

FIG. 5. External cardiac stimulation at very rapid rates (pig). *A*. Control electrocardiogram before stimulation. *B*. Stimulation at 500/min. produces a ventricular response, V, and a pulse wave with every stimulus, E. *C*. Stimulation at 1000/min. with initial 1:1 and subsequent 2:1 response. *D*. Return of normal sinus rhythm and control blood pressure.

stimuli were of low voltage; nevertheless the effective stimuli and their responses differed in configuration from the ineffective stimuli that were seen in the immediately subsequent period of 2:1 response.

The location of the electrodes, the timing of the electric stimulus in the cardiac cycle, and the intensity of stimulation determine whether the externally paced response is supraventricular or ventricular in origin. With high location of the electrodes in the esophagus or on the chest, stimulation produces supraventricular beats; with lower positions the beats are ventricular; at intermediate positions both types of responses may occur. Stimuli occurring early in the responsive phase of the cardiac cycle produce supraventricular beats and late ones produce ventricular beats (fig. 2). If the intensity of an early stimulus that produces a supraventricular beat is increased, however, a ventricular complex may occur.

Figure 6 shows the only instance of supraventricular response that has been observed in man. Complete heart block developed during

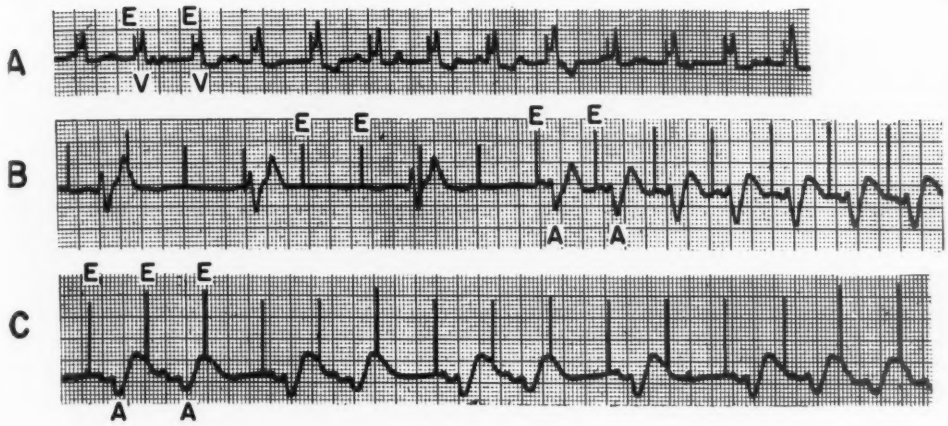

FIG. 6. Ventricular and supraventricular stimulation (man). *A*. Ventricular response, V, to every stimulus, E. *B*. As the stimuli, E, are increased to threshold intensity, the slow idioventricular rhythm is replaced by the faster externally paced supraventricular beats, A. Note the lengthening E-A interval. *C*. Thirteen seconds later a Wenckebach phenomenon has appeared: the E-A interval increases until a beat is dropped and then shortens.

The responses to stimulation in *B* and *C* are supraventricular in origin: (1) they differ in shape from the ventricular responses seen in A; (2) the E-A interval is longer than the E-V interval and is consistent with atrioventricular conduction time; and (3) Wenckebach-type block is a phenomenon of atrioventricular conduction.

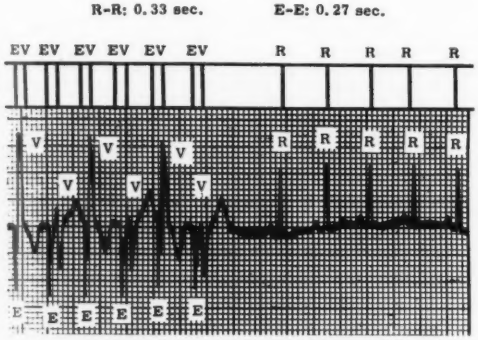

FIG. 7. Bidirectional ventricular complexes produced by external electric stimulation (dog).

cardiac catheterization in an infant with severe cyanotic congenital heart disease and was followed by circulatory collapse. Circulation was maintained for 12 hours by external electric stimulation of the ventricles (fig. 6*A*). Terminally, however, atrial activity ceased and stimulation produced supraventricular beats with a Wenckebach atrioventricular block (fig. 6*B*, *C*).

The ventricular responses to repetitive stimuli may have different electrocardiographic configurations. Infrequent but striking examples are alternating mirror-image complexes (fig. 7), similar to the ominous bidirectional ventricular tachycardia occasionally seen in clinical digitalis intoxication.[18]

The external electric pacemaker generally produces an effective myocardial contraction as well as an electrocardiographic response. The blood pressures depend upon the state of the myocardium and the amount of filling of the ventricles during diastole and not upon whether the pacemaker is intrinsic or external, supraventricular or ventricular. At similar rates the blood pressures following externally paced beats are comparable with those from the intrinsic cardiac pacemaker (figs. 4 and 13*C*).

Recently Starzl, Gaertner, and Webb have concluded from experiments in dogs "that ventricular stimulation in the face of an intact conduction system is injurious."[19] The one published electrocardiogram supporting this conclusion (their fig. 1*c*) shows irregular ventricular beats and arterial pulses during electric stimulation and is clearly just another example of competition between the sinoatrial and the electric pacemaker (our fig. 3). As these authors

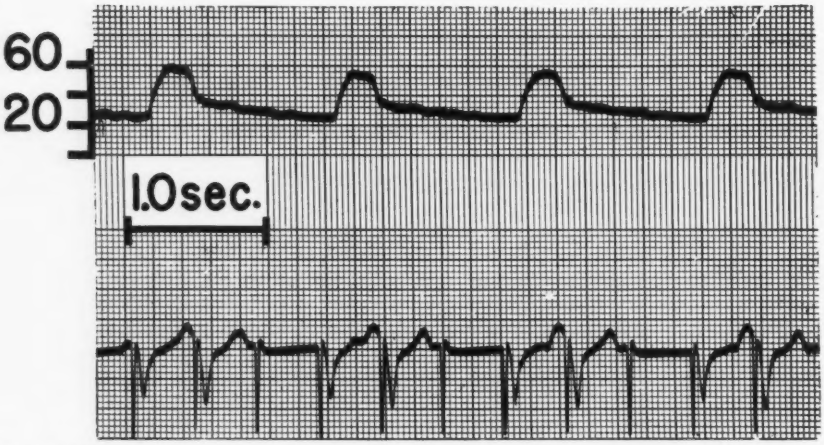

FIG. 8. Dissociation of electric and contractile cardiac responses to stimulation. Threshold stimulation in a dying pig produced electrocardiographic ventricular responses to only 2 of any 3 consecutive stimuli. An effective myocardial contraction with a pulse wave followed only 1 of these 2 electric responses.

themselves illustrate (their fig. 1*d*), however, stimulation at faster rates provides complete control of the ventricular rhythm and regular pulses. Their sweeping condemnation of ventricular stimulation in the presence of an intact conduction system is unwarranted, since it is based on the special circumstance of competition. During normal sinus rhythm in dogs, pigs, and man, external stimulation has taken over control of the heart and produced an effective circulation. Contrary to the suggested hazard of external cardiac stimulation in the presence of atrioventricular conduction,[19] we have observed in dogs with normal sinus rhythm that effective circulation was maintained continuously without ill effect for many hours by the external electric pacemaker.

In the presence of myocardial depression from drugs, shock, anoxia, or myocardial ischemia, an effective myocardial contraction may not always follow every electrocardiographic ventricular response to external electric stimulation (fig. 8). This dissociation of electric and contractile activity is comparable to that seen in the dying heart when the intrinsic pacemaker produces action currents that do not evoke effective myocardial contractions.

No untoward cardiac effects of external electric stimulation were observed in hundreds of animal experiments and in over 70 patients. It did not produce multiple ectopic ventricular beats or ventricular fibrillation, although these disturbances are seen experimentally when electric stimulation is applied directly to the heart. Postmortem examinations in 12 patients and numerous animals showed no evidence of damage from the electric current to the heart or to neighboring structures. The only tissue damage from electric stimulation consisted of superficial ulcerations under the chest electrodes in patients treated for a day or more. This problem has been minimized by frequent small changes in the positions of the electrodes and meticulous care of the skin. The major untoward effects were chest pain and muscular twitch. The intensity of the pain and of the muscular contraction varied in different patients; in some it was negligible, in others it made continued stimulation difficult. Meperidine (Demerol) hydrochloride or paraldehyde usually made the discomfort tolerable and permitted continued stimulation. With prolonged stimulation the severity of the pain usually diminished markedly and less medication was required.

Electric stimulation has been clinically useful in cardiac arrest by producing an externally controlled ventricular rhythm in patients with Stokes-Adams disease, drug-induced standstill, reflex vagal standstill, and arrest occurring u

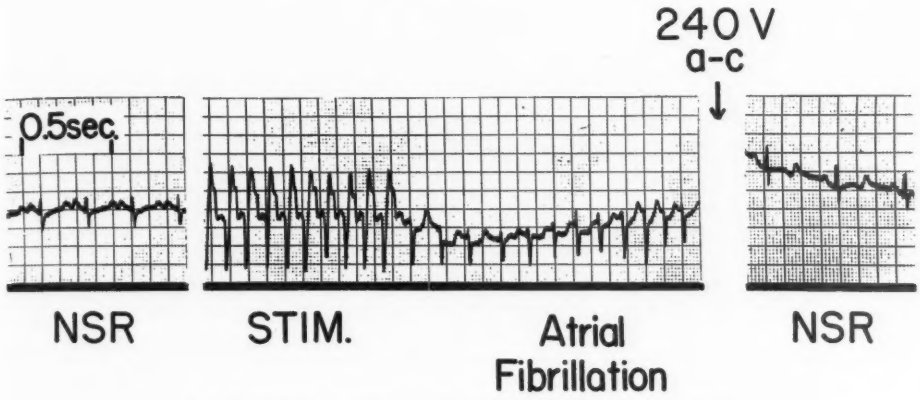

FIG. 9. Induction and termination of atrial fibrillation (dog).

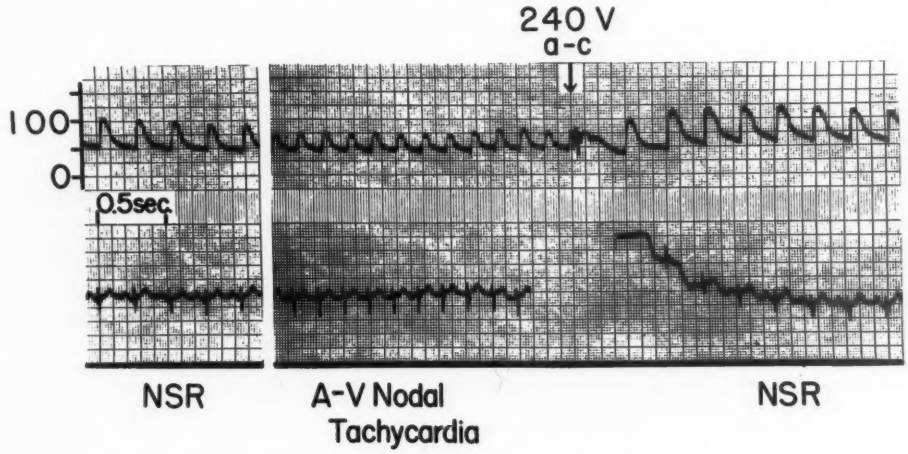

FIG. 10. Induction and termination of atrioventricular nodal tachycardia (pig).

expectedly during various procedures particularly under anesthesia.[1-5]

INDUCTION OF ARRHYTHMIAS BY RAPID STIMULATION

External stimulation of the heart at rapid rates of 500 to 1200/min. for periods of 10 to 60 sec. was applied to normal dogs, normal pigs, and pigs with previous ligation of the left circumflex coronary artery.

In the normal dogs, cessation of rapid stimulation was usually followed by return of normal sinus rhythm. Infrequently, however, atrial fibrillation followed (fig. 9). When rapid stimulation with consequent severe hypotension was prolonged (30 to 60 sec.), ventricular fibrillation often ensued, probably as a result of the marked cardiac ischemia. No other arrhythmias were observed in the dogs.

In 4 normal pigs, no arrhythmias were produced on repeated trials. In a fifth normal pig that was subjected to more prolonged stimulation with shorter rest intervals, 1 episode of ventricular tachycardia and many episodes of ventricular fibrillation were produced.

In 12 pigs, the terminal portion of the left circumflex coronary artery was ligated. Thereafter, atrial, nodal (fig. 10), and ventricular (fig. 11) tachycardia and atrial and ventricular fibrillation (fig. 13*A*) were readily produced by external stimulation. These arrhythmias were induced 88 times between the second and

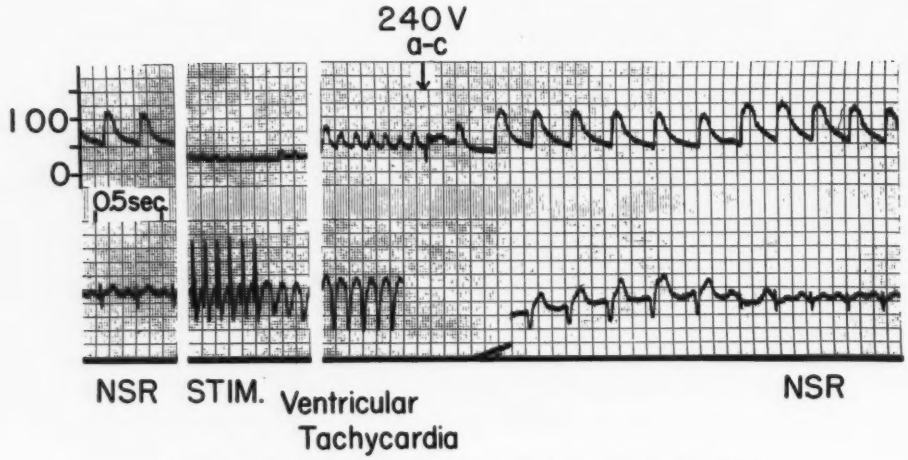

FIG. 11. Induction and termination of ventricular tachycardia (pig).

TABLE 1.—*Induction and Termination of Cardiac Arrhythmias in Pigs with Coronary Artery Ligation*

Type of Arrhythmia	Induction		Termination	
	Without stimulation*	With stimulation	Spontaneous	Countershock
Supraventricular tachycardia	1	6	0	7
Atrial fibrillation	0	13	8	5
Ventricular tachycardia	2	37	15	24
Ventricular fibrillation	1	32	1	32

* Severe anoxia, intracardiac epinephrine, or intravenous procaine amide was probably responsible for these 4 instances.

twenty-eighth day after ligation (table 1). Numerous transient episodes of arrhythmia of less than 10 beats' duration were not included in the tabulation. The episodes of atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia lasted as long as 189 sec.; they terminated spontaneously or were stopped by electric countershock. Ventricular fibrillation was observed to stop spontaneously only once.

The type of arrhythmia that was produced did not appear to be related to the rate or duration of stimulation. We have not investigated all the experimental conditions nor the fundamental mechanisms whereby these arrhythmias were induced by rapid cardiac stimulation.

TERMINATION OF ARRHYTHMIAS BY COUNTERSHOCK

We have stopped each kind of induced arrhythmia in the animals by the application of 60-cycle alternating current of 180 to 660 volts for 0.15 sec. across the closed chest.

Ventricular fibrillation was instantaneously terminated 69 times in dogs and 32 times in pigs. On numerous occasions defibrillation was unsuccessful because of inadequate countershock voltages, improper electrode placement, or poor condition of the animal from prolonged circulatory arrest or excessive countershocks. When the high-voltage countershocks were applied in rapid succession without adequate rest intervals, clear evidence of cardiac damage was manifested by abnormal QRS complexes, fall in arterial pressure, spontaneously recurrent fibrillation, and actual "cooking" of the heart muscle. Similar observations on external defibrillation have been made by others.[11-15]

Furthermore, we have been able to terminate experimentally induced atrial, nodal, and ventricular tachycardia and atrial fibrillation by externally applied countershock (table 1). Although many of these arrhythmias stopped spontaneously, the efficacy of external countershock in terminating them was clearly established by the repeated observation of their instantaneous cessation upon application of the current (figs. 9–13). When countershocks of 180–300 volts were applied, termination of the

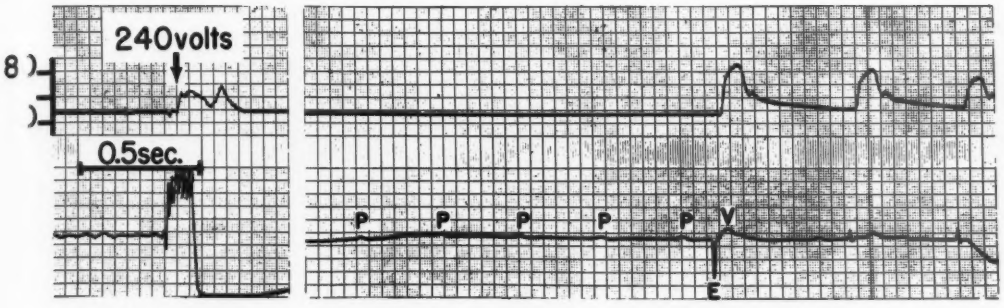

FIG. 12. Termination of postdefibrillation ventricular standstill by a single electric stimulus (pig).

arrhythmias was usually followed immediately by normal sinus rhythm. When higher voltages (300–660 volts) were used, atrial standstill, ventricular standstill, idioventricular beats, or atrioventricular block was often observed. These manifestations of interference with impulse formation and conduction were usually followed quickly by normal sinus rhythm.

In a few instances, ventricular standstill persisted following countershock, especially in hearts depressed by anoxia, prolonged circulatory collapse, or repeated high-voltage countershocks. Under such circumstances external electric stimulation often aroused effective ventricular responses and was followed by spontaneous ventricular activity. Figure 12 shows a sequence, repeatedly observed in 1 pig, of ventricular standstill after defibrillation, in which a *single* effective electric stimulus initiated spontaneous ventricular activity with subsequent resumption of normal sinus rhythm. Figure 13 illustrates prolonged ventricular standstill following countershock and final resuscitation by external electric stimulation and sympathomimetic drugs after 7 minutes of circulatory arrest.

External countershock defibrillation has also been accomplished in the human heart 12 times in 5 patients.[21] In 2 patients ventricular fibrillation followed an acute myocardial infarction. After delays of at least 5 and 7 min. the ventricular fibrillation was terminated instantaneously by countershocks of 240 and 360 volts. Persistent ventricular standstill followed in both cases, however, and heart beats could not be stimulated by the external electric pacemaker.

The third patient had an irregular tachycardia and circulatory collapse for over 15 min., when ventricular fibrillation ensued. After 1 minute of ventricular fibrillation, external electric countershock was applied. Initial shocks of 240 and 360 volts were ineffective. On 6 occasions thereafter, countershocks of 480 to 720 volts defibrillated the ventricles (fig. 14). Each time, however, fibrillation recurred within 2 to 30 sec., following periods of cardiac standstill or ventricular beats. Adequate respiratory exchange was not effected, circulatory collapse persisted, and the patient died.

The fourth patient developed ventricular tachycardia and then ventricular fibrillation as a result of digitoxin overdosage. External countershock of 240 volts stopped the fibrillation. A ventricular rhythm ensued and persisted for 5½ min., but the patient remained apneic, unresponsive, and pulseless, and then died.

The fifth patient had active Stokes-Adams disease. He was resuscitated from ventricular fibrillation on 3 occasions by external countershocks of 270 to 360 volts. Tachycardia occurred twice after defibrillation; once it stopped spontaneously, and once it was terminated by countershock. Ventricular standstill occurred in each episode and external electric stimulation evoked effective ventricular beats, which were followed shortly by spontaneous ventricular rhythm and complete recovery.

These high, potentially dangerous countershock voltages have been applied without accident to the medical personnel. The procedure also appeared safe for the subject; no neurologic sequelae, or cardiac or local tissue

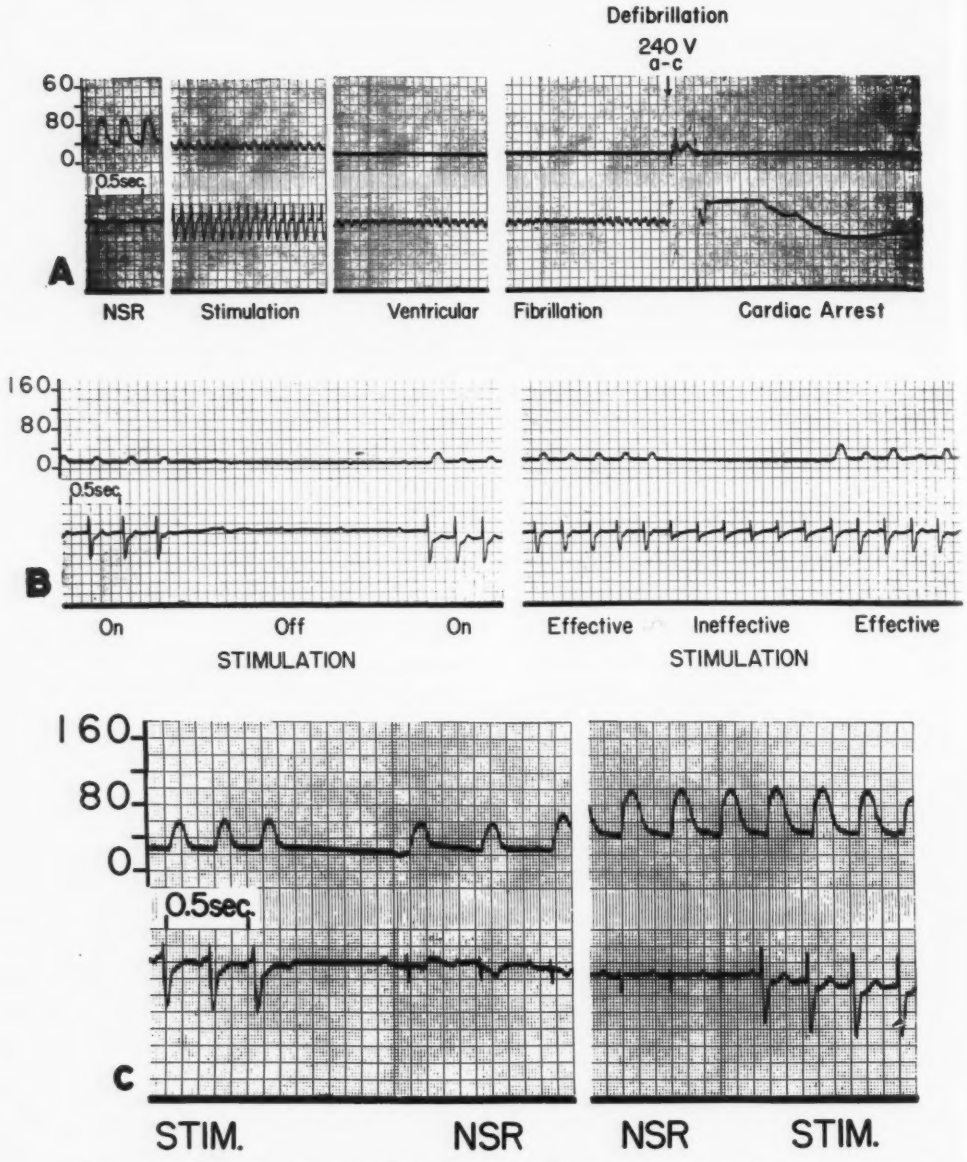

FIG. 13. Induction of ventricular fibrillation, defibrillation, and resuscitation from subsequent cardiac arrest (pig). *A*. Ventricular fibrillation was induced by rapid stimulation (600/min.), persisted for 2 minutes, was terminated by 240-volt countershock, and was followed by cardiac arrest. *B*. External electric stimulation applied during the period of arrest produced ventricular responses and increasing arterial pulse pressure. The dependence of these responses on the external cardiac pacemaker is shown by their disappearance with interruption of stimulation or with reduction of its voltage to ineffective levels. *C*. Seven minutes after the onset of ventricular fibrillation, during a test interruption of external stimulation, normal sinus rhythm returned. Early and later in the recovery period, the external pacemaker produced beats with pressures equal to those from the sinoatrial pacemaker.

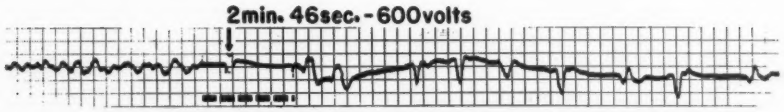

FIG. 14. External countershock defibrillation in man. Ventricular fibrillation was stopped 2 min. 46 sec. after onset by 600-volt countershock, was followed by ventricular beats for 30 sec., and then recurred. The horizontal interrupted line indicates a 1½ sec. interval during which countershock was applied while the electrocardiographic recording was interrupted with the "Instomatic switch."

damage was observed in numerous animals and in the 1 surviving patient.

The termination of atrial fibrillation and supraventricular and ventricular tachycardia by this technic has wide clinical potentialities. External countershock may prove useful in desperate cases resistant to drug therapy, by providing a means of immediate termination of the arrhythmia without the dangers of massive drug dosage.

The demonstrated efficacy of external countershock in stopping ventricular fibrillation in man provides a readily available and safe technic for stopping this usually fatal arrhythmia. Outside the operating room and in seriously ill patients in whom thoracotomy and cardiac massage are particularly inadvisable,[22] external countershock may offer the only effective therapy. In the operating room, external electric stimulation and defibrillation comprise a *combined* technic whereby patients with unexpected cardiac arrest may be resuscitated from ventricular standstill or fibrillation before recourse to the more formidable and traumatic procedure of cardiac massage. Continuous cardiac monitoring* in the operating room would enhance the likelihood of successful external resuscitation by providing immediate recognition of the onset and mechanism of the arrest.

SUMMARY

Electric stimuli applied externally across the unopened chest produced effective cardiac beats and controlled cardiac rhythm in dogs, pigs, and man. Supraventricular and ventricular tachycardia and fibrillation have been readily induced by very rapid external electric stimulation (over 500/min.) in pigs with previous coronary artery ligation. Countershock electric current applied externally has instantaneously terminated all these arrhythmias. Resuscitation of patients from ventricular standstill and ventricular fibrillation by these external technics has been accomplished.

SUMMARIO IN INTERLINGUA

Stimulos electric, applicate externemente a transverso le non-aperte thorace, produceva efficace pulsos cardiac e controlava le rhythmo cardiac in canes, porcos, e humanos. Tachycardia e fibrillation supraventricular e ventricular esseva promptemente inducite per le rapidissime electrostimulation externe (plus que 500 per minuta) in porcos con previemente effectuate ligationes del arteria coronari. Le choc contrari effectuate per le application externe de currente electric terminava instantaneemente omne iste arrhythmias. Le resuscitation de patientes ab arresto ventricular e ab fibrillation ventricular esseva effectuate per medio de iste technicas externe.

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The principal innovation of therapy discussed is Wallgren's successful use of beer as a diuretic in heart failure. The author states "I can think of many patients who will welcome this news."

McKUSICK

Quinidine as a Cause of Sudden Death

By GEORGE W. THOMSON, M.D.

Sudden death and arterial embolism are unpredictable hazards of quinidine therapy for atrial fibrillation that act as deterrents to its most effective use. In this paper an attempt is made to determine the incidence of these accidents as reported in the literature. The mechanism of sudden death is also examined. The difficulty of determining the role of quinidine in producing these accidents in seriously ill patients is clarified.

SUDDEN death and embolism have long been feared as major hazards of quinidine in the treatment of atrial fibrillation. Isolated reports of untoward reactions began to appear shortly after the introduction of the drug by Frey in 1917. Viko, Marvin, and White[1] compiled the first sizable group of cases in 1923 dealing with this problem. In 484 patients, they reported 9 sudden deaths, 6 of which were presumed to be due to embolism. The over-all incidence of embolism, fatal and nonfatal, was 3.1 per cent; the incidence of sudden death was 1.8 per cent. In 1929, Parkinson and Campbell[2] reported on the basis of 554 cases a 4 per cent incidence of sudden death. This latter figure has been generally accepted as the standard risk. In contrast to the emphasis placed on embolism in the earlier report, they noted that "hardly any of these deaths were proved due to emboli, and in most of them necropsy showed no obvious structural disease to account for it [death]". The most recent statistical data were presented by Askey[3] in 1946. He reported on 839 cases, segregated into patients with and without congestive heart failure. Of 275 patients in failure, the incidence of death during treatment with quinidine was 4.0 per cent; in 564 cases not in failure, the incidence was 1.8 per cent. Although no such separation was made in the preceding reports, congestive heart failure was believed to play an adverse role. More recent authors have suggested that the hazards of embolism have been overemphasized, and that sudden death, though a possibility, is rare.[4] In the face of these conflicting data and impressions, it was believed that a review of more recent experiences was in order.

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National Heart Institute Trainee at Lenox Hill Hospital, N. Y., 1953–1954.

REVIEW OF REPORTED EXPERIENCES, 1947–1954

Accordingly, 611 previously uncollected cases have been reviewed from 1947 to the end of 1954. The data given here are based on the experiences presented in 12 major reports, and are limited by their scope.[5-16] Patients were generally unselected as to the underlying cause of heart disease, its severity, the presence or absence of congestive heart failure, the duration of atrial fibrillation, or the association of other disease processes. Attention devoted to these details was so infrequent and involved so few cases that little of statistical significance about these variables was revealed.

In this group of 611 cases, 20 deaths occurred during therapy and were variously interpreted by the several authors. In the interests of uniformity all 20 deaths were arbitrarily regarded in this review as being caused by quinidine. The mean fatal incidence was 3.3 per cent. Clearly, in certain cases death could be attributed to other causes, making the adjusted death rate 2.1 per cent. This compares with Askey's[3] over-all incidence of 2.5 per cent. This adjusted death rate of 2.1 per cent may be regarded as the maximal risk of sudden death from quinidine in this series. Table 1 reveals the wide range of total deaths in proportion to the total number of cases in various hands. The crude death rate varied from 10 per cent in 1 series[15] to no deaths in 2 series.[8, 9] In the largest group of 111 cases, the incidence of death was 0.9 per cent.[4] It was impossible to collect control series of sudden deaths in patients with atrial fibrillation who were not

TABLE 1.—*Deaths During Therapy with Quinidine* (1947–1954)

Series	Total Cases	Total Deaths	Clinical and pathologic findings
Saland[5]	24	1	Rheumatic heart disease. Enlarged heart, mitral insufficiency, mitral stenosis, menorrhagia, found dead in bed. Necropsy: No thrombi found, adenocarcinoma of uterus.
Goldman[6]	48	1	"Sudden death." Necropsy: "No obvious cause of death."
Fleischmann[7]	34	1	*Rheumatic heart disease. Severe mitral stenosis, died in sleep. Necropsy: Severe mitral stenosis, ball type left atrial thrombus, no emboli.
Holzman[8]	57	0	—
Kalmansohn[9]	13	0	—
Sokolow[4]	111	1	Rheumatic heart disease. Severe mitral stenosis, developed ventricular tachycardia and ventricular fibrillation during therapy. Necropsy: "No explanation for sudden death."
McMillan[10]	50	3	*Rheumatic heart disease. Death apparently due to pulmonary edema. Necropsy: Rheumatic pericarditis, mitral stenosis, congestive heart failure. Rheumatic heart disease. Died 2 days after conversion. Necropsy: Right atrial thrombus, fresh and old multiple small pulmonary infarcts, thrombosis of superior mesenteric artery. No data given. No necropsy.
Belaval[11]	14	3	*Died 30 days after conversion from bilateral lobal pneumonia and advanced nephrosclerosis, verified by necropsy. *Severe hypertensive. Died several days after conversion in uremic frost. No necropsy. Hypertensive. Died suddenly at home four hours after leaving hospital against advice. Not converted. No necropsy.
Yount[12]	80	1	Severe congestive heart failure, died suddenly, no necropsy.
Goldman[13]	80	1	Rheumatic heart disease. Died suddenly in bed, half hour after last seen. Necropsy: Mitral stenosis, no pathologically evident cause of death.
Feigin[14]	33	1	*Arteriosclerotic heart disease. Died suddenly at home. Necropsy: "Acute myocardial infarction due to coronary thrombosis."
Bedard[15]	67	7	Arteriosclerotic heart disease. Died suddenly on maintenance dose. No necropsy. Arteriosclerotic heart disease. Died suddenly on day of conversion. No necropsy. Arteriosclerotic heart disease. Died suddenly. No necropsy. Rheumatic heart disease. Developed left hemiparesis, followed by coma and died after several embolic episodes. No necropsy. Arteriosclerotic heart disease. Developed right hemiparesis on relapse to atrial fibrillation, died in coma. No necropsy. *Arteriosclerotic heart disease. Death due to bronchopneumonia confirmed by necropsy. *Arteriosclerotic heart disease and psychosis. Died three weeks after conversion. No necropsy.
Total	611	20	10 cases examined by post-mortem. One death proved pathologically due to embolism.

Total incidence of death among patients receiving quindine = 3.3%.
Adjusted incidence where death could be reasonably ascribed to other causes = 2.1%.
* Death from causes other than quinidine therapy.

receiving quinidine, partly because of the difficulty in deciding the cause of death. This difficulty also applies to the 20 patients who died suddenly while they were receiving quinidine.

In the majority of the 20 deaths reported, death occurred suddenly; patients were either observed to die suddenly or were found dead unexpectedly (table 1). Almost half of the deaths occurred in rheumatic patients with

mitral stenosis. In 10 cases where pathologic examination was permitted, embolism was implicated only once. This patient had rheumatic heart disease and died in pulmonary edema. Necropsy revealed multiple small pulmonary infarcts, fresh and old, and thrombosis of the superior mesenteric artery. In 2 cases without postmortem examination, undoubted cerebral embolism with hemiplegia occurred, followed by death in coma. The infrequency of pathologically verified embolism as a cause for sudden death is provocative. However, in none of the 10 cases necropsied was it specifically stated that examination of the brain was performed; no pathologically evident cause of death could be found, nor could embolism be implicated from evidence of intracardiac thrombi of peripheral emboli in 5 cases. In the remaining 5, the cause of death was determined at necropsy as indicated in table 1. On the other hand, where nonfatal embolism was observed, the brain was the most frequent site, manifested by signs of hemiplegia and aphasia. From the available data, in accord with the experience of Parkinson and Campbell,[2] we are inclined to comment on how frequently no pathologically evident cause of sudden death could be found. However, valid conclusions regarding the cause of sudden death cannot be drawn from the limited necropsy data available; similarly, the inference of cerebral embolism does not seem warranted in view of these limitations.

Embolism was recognized clinically in 11 patients in a subgroup of 418 where the presence or absence of embolism was specifically noted (table 2). This is a clinical incidence of 2.3 per cent. Despite the notion that embolism most

TABLE 2.—*Occurrence of Embolism in Patients Under Treatment*

Series	Total	Number with emboli	Anticoagulants	Clinical findings	Relation to conversion	Embolic deaths	Past history of emboli
Saland[5]	24	1	Yes	Pulmonary infarct during therapy.	Remained in atrial fibrillation	0	15
Goldman[6]	48	2	No	Right hemiplegia, in one case; sensory aphasia in another.	Both at conversion.	0	10
Fleischmann[7]	34	0	Not stated	—	—	0	9
Sokolow & Edgar[16]	30	0	Not stated	—	—	0	2
Belaval[11]	14	0	No	—	—	0	1
Yount[12]	155	2	Not stated	—	—	0	23
Goldman[13]	80	3	Yes	1. Pulmonary infarct. 2. Motor aphasia. 3. Left hemiparesis.	1. On relapse to atrial fibrillation. 2. 48 hours after conversion. 3. "Hours" after conversion.	0	Unknown
Feigin[14]	33	0	Yes	—	—	0	Not stated
Bedard[15]	67	3	Not stated	1. Left hemiplegia, coma, death; no necropsy. 2. Right hemiplegia, coma, death; no necropsy. 3. No data.	1. Never converted. 2. One day after relapse to atrial fibrillation. 3. No data.	2	Not stated
Total	485	11					

Over-all incidence of embolism during treatment = 2.3%
Incidence of clinically defined embolic deaths = 0.4%

frequently occurs on resumption of normal sinus rhythm, when the time of occurrence of embolism was noted in 8 cases, it occurred twice at conversion, twice sometime after conversion, twice during continued fibrillation, and twice on relapse to fibrillation after prior conversion to normal sinus rhythm.

The results of giving quinidine to patients with established fibrillation in whom embolism had previously occurred were interesting. Sir Thomas Lewis[17] regarded previous embolism as an absolute contraindication to the use of the drug. However, there has been a gradual evolution of a different opinion. By 1944, the National Research Council[18] listed the history of systemic embolization in paroxysmal or established fibrillation as an indication for treatment with quinidine. Of 230 cases reviewed where the presence or absence of previous embolism was noted, 79 patients had previous embolic accidents. During treatment with quinidine, only 1 of these 79 suffered a second embolization, and this occurred on relapse to fibrillation. He was again converted, and remained symptom-free in sinus rhythm for a follow-up period of 9 months. Embolism however occurred in 6 patients who had no previous episodes. It would appear, therefore, that previous embolism adds a negligible embolic hazard to quinidine therapy.

The frequency of intracardiac thrombi and systemic and pulmonary embolism in the presence of fibrillation has been long appreciated. However, only recently has regularization of rhythm by quinidine as a means of preventing embolism received much attention. Saland and co-workers[5] selected 15 cases in a group of 24 with an embolic history as an indication for quinidine treatment. They reported good immediate results, although no long term follow-up was available. Yount[12] reported no further emboli after conversion in 23 patients in whom previous embolism had occurred. Occasional dramatic results with longer follow-up observations have been reported in individual cases with repeated or multiple embolization threatening life. Parkinson and Campbell[2] mentioned a patient with rheumatic cardiac disease who suffered 3 successive major embolic events and who, after conversion to normal rhythm, remained free of recurrence for 5 years. Sokolow[19] reported a patient with multiple emboli, who remained symptom-free for 1 year in sinus rhythm. White and Blumgart[20] converted a 49-year-old rheumatic patient exhibiting recurrent multiple pulmonary emboli with increasing heart failure, who was free of congestion and embolism 5½ years thereafter. There has been a general impression among recent authors of the protective effect against embolism of sinus rhythm, although more long-term observations are needed.

In the matter of concurrent use of anticoagulants with quinidine, only meager data are available. In a group of 137 patients so treated (table 2), 4 suffered embolism. In a "control" group of 348, 7 embolic accidents occurred. Statistically significant conclusions obviously cannot be drawn.

TABLE 3.—*Death Rate in Relation to Dosage*

Total cases	Dosage	Deaths	As per cent of cases
203[9, 12, 13, 16]	Limited by arbitrary plasma quinidine levels.	2	0.98
188[6, 8, 10, 14]	Arbitrary point, beyond which no drug given.	5	2.6
105[5, 11, 15]	No stated arbitrary upper limit, or given until toxicity or conversion.	11	10.6

DISCUSSION

It is apparent that the risk of sudden death from quinidine is real, and in some cases it is not susceptible to pathologic explanation. No final conclusions regarding the cause of sudden death can be made because of the limitations of the reported necropsy material. The available data favor some reason other than embolism. Certainly several known factors are operative. The nature and the severity of the underlying heart disease, of associated serious illness such as lobar pneumonia, uremia, and recent severe hemorrhage, and senile debility appear on occasion to affect the result (table 1). Of most concern, however, is the occurrence of sudden death in the relatively well patient. It may be possible to reduce the number of such catastrophies.

An analytic approach to the problem suggests that uncontrolled dosage may be a significant lethal factor (table 3). It is widely recognized that idiosyncrasies manifest by profound circulatory collapse, leading sometimes to a fatal outcome, do occur on small doses of the drug and at low plasma levels. Since dosage is not sharply defined, the total dose and the time over which it is given reflect, among other things, the prevailing local conceptions of the drug's mode of action and toxicity and the evaluation of the clinical situation. But most important of all appears to be the care exercised in the control of dosage, which amounts to the frequency with which observations of one or another type are made on the patient while he is receiving large doses of the drug. Table 3 indicates that the mortality may be greater where no limits on the amount of the drug are set.

The occurrence of serious ventricular arrythmias during quinidine therapy has been well documented.[25, 31, 42, 44, 45, 47, 48] Ventricular tachycardia and fibrillation appear to have been noted with greater frequency than cardiac standstill, although the latter has been recognized electrocardiographically as a terminal event on occasions when quinidine has been given intravenously to control ventricular tachycardia.[49] Coma, convulsions, and altered states of consciousness described during the course of aberrant ventricular rhythms are undoubtedly related to the failure to maintain an adequate cardiac output and adequate cerebral blood flow. Seven such fatal reactions were reported following intravenous administration of the drug, and conduction defects such as complete bundle-branch block or intraventricular block appear to add to the hazards.[21] Similarly, ventricular tachycardia has been reported to occur with the use of quinidine in atrial fibrillation associated with complete atrioventricular dissociation.[45]

Also pertinent to the problem is the reported occurrence of events, similar in nature to idiosyncratic reactions to the drug, which may become manifest only with high plasma quinidine levels or large or frequent doses of the drug.[9] A generally unappreciated phenomenon is the apparent effect of quinidine as an excitant and at times depressant of the vital centers of the central nervous system.[21] Acute studies of toxicity in animals indicate that severe depression of respiration occurs with apnea, followed by circulatory collapse. This reaction can be reversed with vasopressor drugs, artificial respiration, and central nervous system stimulants.[22] Comparable reactions have been observed in man.

Kalmansohn[9] lists precipitant hypotension as the chief contraindication for continued use of the drug, since it frequently heralds the onset of circulatory collapse. Ferrer and co-workers[23] found significant hypotensive reactions with a single 0.8 Gm. dose of the drug. These were seen in control patients with normal cardiac output and normal right ventricular end-diastolic pressure, so that a myocardial effect could be excluded.

In retrospect, it is of interest that Frey in 1921 in his early reports of toxicity listed cases of respiratory paralysis successfully revived by artificial respiration and central nervous stimulants.[24] One year later, Levy[25] reported 4 cases of sudden collapse with unconsciousness marked by temporary cessation of heart beat and respirations, with recovery. Clarke-Kennedy[26] reported a fatal reaction in 1922 in which "sudden unconsciousness, apnoea, pulselessness, and profound cyanosis" occurred 16 hours after conversion. In a somewhat similar experience in recent years massive intravenous doses of quinidine provoked a sudden collapse with "complete unresponsiveness, cessation of breathing, and heart sounds" with successful revival by neosynephrin, caffein, and oxygen and eventual complete recovery.[27]

Berman and co-workers[28] in 1953 reported a unique case among 5 cases of severe untoward reactions. This patient developed a convulsive state followed by apnea, cyanosis, and pulselessness after quinidine was given; recovery subsequently occurred. The reaction was unwittingly reproduced by a second dose and led to a fatal outcome. No cerebral embolism or obvious cause of death was demonstrated on postmortem examination. These authors[28] suggest that convulsions, respiratory failure, circulatory collapse, and absent blood pressure represent a syndrome of "quinidine shock,"

TABLE 4.—*Analysis of Thirty-two Sudden Deaths Reported Before 1947*

Source	No. of Cases	Age	Sex	Clinical data	Manner of death	Necropsy	Evidence of embolism
Viko, Marvin, White[1]	2	—	—	None given	Both sudden	No	—
Burwell and Dieuaide[29]	1	22	F	RHD, EH, MS, AI	Sudden	No	—
Kohn and Levine[30]	3	44	F	RHD, MD	Groaned and found dead.	Thrombus in left atrium	No emboli found
		20	M	RHD, MI, MS	Suddenly groaned, cyanotic, respirations ceased.	No	—
		64	M	Chronic myocarditis	Suddenly dyspneic, unconscious, died in bizarre rhythm.	No	—
Parkinson and Campbell[2]	2	—	—	No data given	Both sudden	Yes	No emboli found
Newman and Spiro[31]	1	40	—	RHD, MS	Sudden	No	—
Clarke-Kennedy[26]	1	—	F	RHD, MS, hypertension	Sudden	Yes*	No emboli found
Smith and Boland[32]	3	45	F	RHD	Ceased talking and died.	No	—
		57	M	Thyroid adenoma, AF	Sudden	Yes	None
		53	M	Hypertensive and ASHD	Sudden	Yes	None
Jamieson[33]	4	—	M	AF of unknown cause	Sudden	Yes*	None
		29	F	RHD, MS, CHF	—	No	—
		60	M	SHD, EH, AI, syphilitic aortitis, CHF	Sudden	Yes	None
		70	M	HHD & ASHD, CHF	Sudden	Yes*	None
Smith and Clarke[34]	1	22	F	RHD, EH, MI	Muscle twitching; rapidly dyspneic, cyanotic, and died.	No	—
Hay[35]	6	—	—	No clinical heart disease	Died suddenly	Apparently none	—
		30	F	RHD, MS	Suddenly apneic, died	No	—
		55	M	No diagnosis	Sudden	Apparently none	—
		34	F	No diagnosis	Sudden	Apparently none	—
		—	F	Paroxysmal tachycardia	Sudden	No	—
		27	M	RHD, EH, MS	Sudden	Yes*	None
Maynard[36]	1	—	F	AF of unknown cause	Respiratory difficulty, unconscious; heart beat continued, then died.	No	—
Sappington[37]	1	50	M	AF, CHF	Kicking, twitching, became unconscious, died.	No	—
Levy[38]	1	49	F	AF, EH	Became cyanotic, dyspneic, respirations ceased.	Yes	None
Berman and Blumenthal[39]	5	80	M	Coronary disease, hypertensive	Died suddenly	No	—
		60	F	Hypertensive, EH	Sudden	No	—
		67	M	Coronary disease	Sudden	No	—
		70	M	Coronary disease	Found dead	Yes	None
		54	M	Hypertensive, CHF	Sudden	Yes	None

* Autopsy failed to show immediate cause of death.

AF = atrial fibrillation; AI = aortic insufficiency; CHF = congestive heart failure; EH = enlarged heart; HHD = hypertensive heart disease; MD = mitral disease; MI = mitral insufficiency; MS = mitral stenosis, RHD = rheumatic heart disease; SHD = syphilitic heart disease.

which may be brief and responsive to artificial respiration and central nervous system stimulants. They speculate that these reactions "in the past interpreted as cerebral emboli, in reality . . . represent this . . . syndrome, occurring shortly after regularization."

Thirty-two cases in the older literature, where sudden death was specifically stated to have occurred, were reviewed with the view to applying these criteria (table 4). Despite the infrequency of detailed description of the mode of exitus, the possibility of sudden central nervous system depression was suggested in 13 cases as manifested by sudden cyanosis and dyspnea, unconsciousness, apnea, groaning, muscle twitching, and convulsions. In the total group, necropsies in 13 failed to show any embolic phenomena; 3 of these had demonstrated signs of sudden central nervous system depression during life. Although it is possible that primary central nervous system depression reflecting an unappreciated toxic action of the drug may have had a role in the production of sudden death, such cerebral phenomena may also have been secondary to the failure to maintain an adequate cardiac output in clinically unrecognized arrhythmias.

As previously noted, the incidence of death is increased by the presence of congestive heart failure. Evidence exists that the toxicity of quinidine is augmented by the presence of congestive failure. Plasma quinidine tends to persist at high levels and the drug is dissipated slowly.[40] Unusually high serum levels and serious toxicity can occur in contrast to what occurs in normal subjects, or in patients with frank hepatic or renal disease.[41] Further, it has been observed that ventricular tachycardia, as a toxic manifestation of quinidine, occurs more frequently in patients with congestive heart failure.[42] The tendency to toxicity with congestive failure is so imminent that some authors have advised that continued administration of the drug to such patients be controlled by frequent determinations of the serum level.[42]

Summary

. The separate risks of sudden death and embolism during therapy with quinidine are appreciable. In 611 recently reported cases (1947–1954) the over-all death rate was 3.3 per cent. In 418 of these patients, the incidence of clinical embolism was 2.3 per cent. Death due clinically certain cerebral embolism occurred in only 2 cases.

2. In 10 fatalities studied at necropsy, embolism was implicated only once. In the majority, no pathologically evident cause of death could be found. Nearly half of the total deaths occurred in patients with rheumatic heart disease and mitral stenosis.

3. Prior embolism appears to carry a negligible risk of repetition during quinidine treatment.

4. Where no arbitrary dosage limit is set, the mortality appears greater.

5. Severe organic heart disease, congestive heart failure, and associated grave illnesses increase the possibility of a fatal reaction.

6. Unappreciated toxic effects of the drug, especially on the central nervous system, appear to play a role in the production of sudden death ("quinidine shock"). It is suggested that these effects might be avoided by a more judicious selection of patients for therapy and meticulous supervision of all patients receiving large doses.

Acknowledgment

The author is grateful to Charles E. Kossmann, M.D., for his help in the preparation of this paper.

Summario in Interlingua

1. Le duo distincte riscos de morte e de embolismo in therapia a quinidina es appreciabile. In 611 casos reportate inter 1947 e 1954, le mortalitate total esseva 3,3 pro cento. In 418 de iste patientes, le incidentia de embolismo clinic esseva 2,3 pro cento. Morte per embolismo cerebral con certitude clinic occurreva in solmente 2 casos.

2. In 10 mortes studiate necropticamente, embolismo esseva involvite solmente 1 vice. In le majoritate de iste 10 casos, nulle pathologicamente evidente causa de morte esseva constatabile. Quasi un medietate del mortes total occurreva in patientes con rheumatic morbo cardiac e con stenosis mitral.

3. Casos con embolismos de occurrentia

previe pare currer un risco negligibile de repetition durante le tractamento a quinidina.

4. Quando le dosage es sin limites de fixation arbitrari, le mortalitate es apparentemente plus grande.

5. Sever organic morbo cardiac, congestive disfallimento cardiac, e associate morbos de alte severitate augmenta le possibilitate de un reaction mortal.

6. Non-recognoscite effectos toxic del droga, specialmente super le systema nervose central, ha apparentemente un rolo significative in le causation del morte ("choc a quinidina"). Nos opina que iste effectos es possibilemente evitabile per un plus meticulose selection del patientes subjicite a iste therapia e per un detaliate surveliantia del patientes qui recipe grande doses del droga.

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From this view of the different parts of the plant, it is sufficiently obvious why I still continue to prefer the leaves.

These should be gathered after the flowering stem has shot up, and about the time that the blossoms are coming forth.

The leaf-stalk and mid-rib of the leaves should be rejected, and the remaining part should be dried, either in the sun-shine, or on a tin pan or pewter dish before a fire.

If well dried, they readily rub down to a beautiful green powder, which weighs something less than one-fifth of the original weight of the leaves. Care must be taken that the leaves be not scorched in drying, and they should not be dried more than what is requisite to allow of their being readily reduced to powder.

I give to adults, from one to three grains of this powder twice a day. In the reduced state in which physicians generally find dropsical patients, four grains a day are sufficient. I sometimes give the powder alone; sometimes unite it with aromatics, and sometimes form it into pills with a sufficient quantity of soap or gum ammoniac.—William Withering. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

Massive Thrombotic Occlusion of the Large Pulmonary Arteries

By K. P. Ball, M.D., M.R.C.P., J. F. Goodwin, M.D., M.R.C.P., and C. V. Harrison, M.D., P Sc.

In 23 cases of massive thrombotic occlusion of the large pulmonary arteries thrombosis secondary to pulmonary embolism was the major cause, but a proportion (30 per cent) was considered to have primary thrombosis in situ. The pathologic criteria, symptoms, signs, and results of special investigations are given in detail, and the diagnosis, etiology, and precipitating factors are discussed.

PULMONARY heart disease resulting from thrombotic occlusion of the small pulmonary arteries due to repeated emboli has been recognized for some years,[1, 2] and the occurrence of repeated "silent" emboli to the lungs has been reported by Owen and associates.[3]

Massive thrombosis of the large pulmonary arteries is infrequently considered in the differential diagnosis of obscure cases of right-sided heart failure, although over 200 cases have been described in the literature. The first report apparently was that of Hélie in 1837,[4] while Savacool and Charr[5] collected 88 cases from the literature and added 12 of their own. Brenner[6] found 4 cases in 100 unselected autopsies, and Middleton[7] found 53 cases in autopsies over a period of 16 years at the Wisconsin General Hospital. In 5 of the 12 cases of widespread repeated pulmonary emboli reported by Owen and associates,[3] the occlusion involved the large branches of the pulmonary artery. The condition has recently been reviewed by Magidson and Jacobson[8] who have added 7 more cases.

Massive thrombotic occlusion of the main pulmonary arteries has usually been described in association with other diseases, notably pulmonary tuberculosis, carcinoma of the lung, congenital heart disease, and various forms of acquired heart disease. It may, however, occur in the absence of any other disorder, but few cases have been diagnosed in life.

The object of this paper is to present a total of 23 cases, 9 of whom were seen in life, while the remaining 14 were obtained from an examination of 7,000 autopsy records in the the Department of Pathology, Postgraduate Medical School. The diagnosis was made before death in 3 of the 9 patients seen in life, and autopsy confirmation was obtained in all cases.

The diseases associated with thrombosis of the main pulmonary arteries included pulmonary disease (carcinoma of the lung, chronic bronchitis), cardiovascular disease (valvular disease, coronary artery disease, and congenital heart disease), and gastrointestinal disorders. In 4 cases no associated disease was present, although in 3 of these a generalized thromboembolic tendency of unknown etiology was manifested by repeated episodes of venous thrombosis at various sites.

The cases without associated disease will be considered first.

Case Material

Thrombosis of the Main Pulmonary Arteries without Associated Disease

Case 1. A 48-year-old woman developed progressive dyspnea on exertion, followed by syncopal attacks in 1951. In 1952, she was found to have an iron-deficiency anemia and was treated with intravenous iron. During treatment she developed signs of congestive cardiac failure, with peripheral edema, ascites, hepatic pulsation, and an elevated jugular venous pressure. There was a blowing systolic murmur over the pulmonary artery and down the left sternal border, and right ventricular enlargement. Fluoroscopy revealed large pulsating pulmonary arteries.

She subsequently developed thrombosis of the left iliofemoral vein, for which she was treated with dicumarol. Congestive cardiac failure increased and

From the Central Middlesex Hospital, London, and the Departments of Medicine and Morbid Anatomy, Postgraduate Medical School of London and Hammersmith Hospital, London, England.

tricu pid incompetence developed. Thrombosis of the inferior vena cava was suspected. Treatment with digitalis, mercurial diuretics, and ion-exchange resin was without effect during any of her repeated admissions to the Central Middlesex Hospital, and on August 30, 1953, she was transferred to Hammersmith Hospital.

On examination she was an anxious, slightly cyanosed woman with orthopnea and cold extremities. The pulse was of small volume and regular. The jugular venous pressure was raised to 8 cm. above the sternal angle with a large systolic wave, indicating tricuspid incompetence. There was extensive edema. The cardiac impulse was diffuse, tapping, and with sternal pulsation, indicating right ventricular hypertrophy. The second heart sound was normally duplicated and not accentuated. A grade 4 systolic murmur was maximal in the third and fourth left intercostal spaces. The blood pressure was 90/60 mm. Hg. The lungs were clear, and there was ascites. The liver was enlarged and pulsated in systole. The spleen was not enlarged.

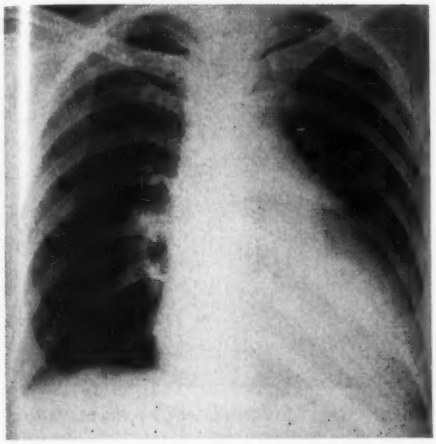

FIG. 1. *Case 1.* Posteroanterior roentgenogram of the chest showing enlargement of the right ventricle, main pulmonary trunk, and right main branch. The lung fields are underfilled.

Chest x-ray and fluoroscopy (fig. 1) showed a large right ventricle, considerable enlargement of both pulmonary arteries, which did not pulsate, and oligemic lung fields. An electrocardiogram showed sinus rhythm, right ventricular, and right atrial hypertrophy (fig. 2). The phonocardiogram showed a systolic murmur maximal in midsystole in the pulmonary area. Liver function tests were normal, except for albumin of 2.6 and globulin of 3.5 Gm. per cent. The blood count was normal, with a hemoglobin of 90 per cent.

On cardiac catheterization the right atrial pressure was 11/6 mm. Hg. The tracing was typical of tricuspid incompetence. The right ventricular pressure was 90/18, with a mean of 35 mm. Hg. The pulmonary artery was not entered. There was no evidence of a septal defect with left-to-right shunt. The arterial oxygen capacity was 94 per cent saturated. The cardiac output by the Fick method was 1.6 L./min. It was concluded that there were right ventricular hypertension, tricuspid incompetence, low cardiac output, and no cardiac shunt.

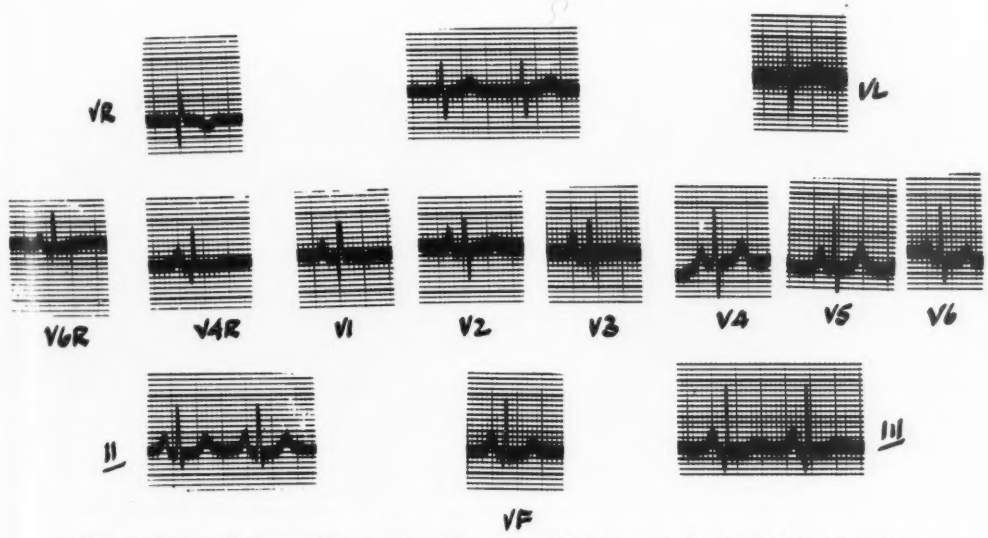

FIG. 2. *Case 1.* Electrocardiogram, showing augmented P waves indicating right atrial enlargement, and qR patterns in leads V_4R and V_1, indicating right ventricular hypertrophy.

The course of the disease was punctuated by episodes of bleeding into the muscles of the thigh, accompanied by thrombocytopenia. The platelet count was 34,000/ml. during the first attack. One week later the white cell count was 20,000/ml. with 84 per cent polymorphonuclear cells and 1 per cent eosinophils, and the hemoglobin fell to 79 per cent. A bone marrow study showed a normal number of platelet-forming megakaryocytes, but an excess of non-platelet-forming types usually associated with thrombocytopenic purpura. The prothrombin time was normal. The initial episode of bleeding resolved slowly, concomitantly with the administration of cortisone. In spite of treatment, cardiac failure steadily increased, accompanied by several paroxysms of atrial tachycardia, followed by atrial fibrillation, and by swelling of the left arm suggestive of an axillary vein thrombosis. Death occurred on November 4, 1953.

The clinical diagnoses were congestive cardiac failure; tricuspid incompetence; thrombosis of the large pulmonary arteries, probably secondary to multiple emboli; inferior vena caval thrombosis; and episodic thrombocytopenic purpura and thrombosis of undetermined cause.

A point of special note was the development of dyspnea and syncope, before the onset of signs of peripheral venous thrombosis and the progressive reduction in pulsation of the enlarged pulmonary arteries on fluoroscopy. This observation suggested that the initial occlusions had occurred in the small pulmonary arteries and spread proximally.

At autopsy both main branches of the pulmonary artery were almost completely occluded by laminated, organizing thrombi, which met half an inch above a normal pulmonary valve (fig. 3). The right ventricle was hypertrophied, but the tricuspid valve

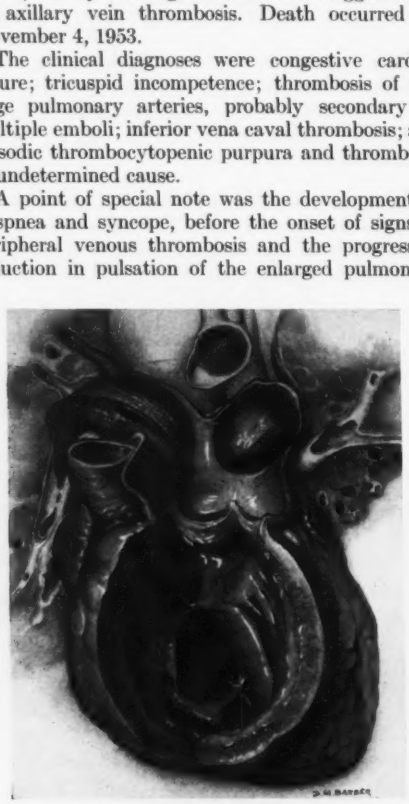

FIG. 3. *Case 1.* Drawing of postmortem appearance of heart and pulmonary arteries. The heart is normal, apart from hypertrophy of the right ventricle. The distal portion of the main trunk of the pulmonary artery and the right and left main branches are filled with adherent thrombus. Many of the smaller arteries are also filled with thrombus, which is traversed by fibrous trabeculae. The pulmonary veins are normal.

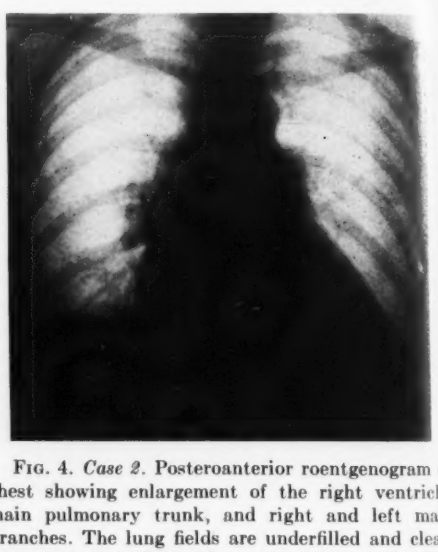

FIG. 4. *Case 2.* Posteroanterior roentgenogram of chest showing enlargement of the right ventricle, main pulmonary trunk, and right and left main branches. The lung fields are underfilled and clear, except for an ill-defined loss of translucency in both costophrenic regions.

FIG. 5. *Case 2.* Postmortem appearance of the heart, pulmonary artery, and lungs. The heart is normal except for hypertrophy of the right ventricle. Both main branches of the pulmonary artery (arrows) contain adherent thrombus, which shows clear evidence of coiling in the left main branch.

was not dilated. The mitral and aortic valves were normal, as were the septa. There was no evidence of thrombosis of the caval, iliac, or femoral veins.

An antemortem thrombus extended into the peripheral branches of the pulmonary artery on both sides, being more recent on the left. No pulmonary infarcts were present. The thrombus in the main pulmonary arteries and their immediate branches was pale and had clearly been deposited in layers. In the smaller arteries the lumina were frequently broken up by fibrous strands into a number of channels, and these in their turn were occluded by recent red thrombi. Histologic examination confirmed that the thrombus in the main arteries had been deposited in layers, of quite different ages, the deeper being well organized and the superficial being relatively recent. There was no evidence of atheroma of any significance and none of arteritis.

The bronchial arteries were more prominent and dilated than normal. The lung parenchyma and bronchi were normal.

The liver was markedly congested and showed changes of early cirrhosis. The bone marrow was normal; the spleen was very congested.

Case 2. A 56-year-old woman began her illness with swelling and tenderness of the calf, followed 1 month later by dyspnea on exertion and orthopnea. Two weeks later she developed pleuritic pain on the right side, and suffered 2 hemoptyses. Death occurred suddenly, despite anticoagulant therapy.

On examination she was a dyspneic, cyanosed woman, with a small regular pulse, elevated jugular venous pressure, and edema of the legs. There was doubtful enlargement of the right ventricle, the second heart sound was normal, and there was a loud systolic murmur over the pulmonary artery. The blood pressure was 140/80 mm. Hg. There was dullness at the base of the right lung, but no clubbing of the fingers.

X-ray film of the chest showed large main pulmonary arteries and right ventricle. The lungs were clear except for an opacity at the right costophrenic angle (fig. 4). (The patient was too ill for fluoroscopy.) Electrocardiogram showed low voltage with first degree atrioventricular block, and doubtful right ventricular hypertrophy.

The clinical diagnosis was thrombosis of main pulmonary arteries, probably secondary to repeated pulmonary emboli.

At autopsy the main pulmonary artery was occluded by an adherent laminated thrombus that showed coiling (fig. 5). No underlying disease of the pulmonary artery was present. The appearances were those of embolism with secondary thrombosis, the age of the thrombus being consistent with the duration of the symptoms. The heart was normal, apart from hypertrophy of the right ventricle. Both femoral veins were thrombosed. No other disease was present.

The diagnosis was suspected in these patients be-

TABLE 1.—*Cases* of Thrombosis of the Large Pulmonary Arteries without Associated Disease*

No.	Sex Age	History	Clinical findings and progress	X-ray	Electrocardiogram	Autopsy findings		Comments
						Description	Infarcts in lungs	
3 MF	F 46	Attacks of fever, substernal pain, hemoptysis, and dyspnea; died suddenly	Signs of venous thrombosis in legs; fluid in right chest; apical systolic murmur; triple rhythm; falling B.P.	Heart enlarged	Left bundle-branch block; large right atrium, ? large right ventricle	Thrombosis of main pulmonary arteries to right lower and upper lobes; dissection shows emboli embedded in local thrombus; histology shows organizing clots; multiple thromboses in leg and arm veins	+	Thrombosis secondary to embolism; generalized thromboembolic disease; ? cause
4 HI	F 79	Admitted because of severe epistaxis; vomited twice; died suddenly 9 days after admission	No abnormal signs; B.P. 130/80; slight albuminuria	—	—	Thrombosis of right and left main pulmonary arteries; recognizable embolus lies in mass of secondary thrombus; histology shows severe pulmonary atheroma; clot lies over atheromatous plaques; no source for embolus	+	Thrombosis secondary to embolism; generalized thromboembolic disease; ? cause

* Cases 1 and 2 discussed in detail in text.

TABLE 2—*Cases* of Thrombosis of the Large Pulmonary Arteries Associated with Mitral Stenosis*

No.	Sex Age	History	Clinical findings and progress	X-ray	Cardiogram	Autopsy findings		Comments
						Description	Infarcts in lungs	
7 DP	F 59	Progressive dyspnea on exertion; paroxysmal dyspnea; hemoptysis	Signs of severe mitral stenosis; sinus rhythm with calcified mitral valve; valvotomy performed; subsequent atrial fibrillation; 5 months after operation succumbed to coronary thrombosis and multiple systemic emboli	LA + RV + PA +	Slight right vent. hypertrophy	Thrombus in left coronary artery with anteroseptal infarct; embolus in right external iliac artery. Thrombus partially occluding right main PA; heavily calcified mitral valve with tear in one commissure	0	A local thrombosis in the PA overlying a patch of atheroma (fig. 8)
8 TF	M 18	Dyspnea on exertion; hemoptysis; jaundice; fever; stabbing pain in the chest; died suddenly	Signs of mitral stenosis and tricuspid incompetence; systolic murmurs at apex and tricuspid area, due to mitral and tricuspid disease respectively; rales over right lung; sinus rhythm, jaundice	Heart enlarged; opacity at base of right lung	RA + RV +	Mitral and tricuspid stenosis, thrombosis of right main PA; no source for emboli found	Massive right lung	Probably repeated pul. emboli but thrombus not coiled in PA; impossible to tell origin pathologically
9 JS	M 77	Sudden ischemia of left foot due to arterial embolus	Atrial fibrillation; gangrene of left foot; no heart failure or cardiac murmurs detected; died in coma due to cerebral vascular accident	—	Ischemic pattern	Occlusion of left femoral artery; mitral stenosis; thrombosis right PA; lower lobe artery contained a thrombus, which took the shape of, and filled the artery; histology showed laminated thrombus; no source for emboli	1 small	Probably thrombus in situ
10 RF	F 80	Progressive dyspnea; confusion; old cerebral embolism; bedridden	Mitral stenosis; aortic incompetence; atrial fibrillation; anemia; old hemiplegia	—	—	Mitral stenosis; aortic incompetence; small myxoma of left atrium; adherent laminated organized thrombus partially occluding right PA; also, recent pulmonary embolus with infarct in right upper lobe; thrombosis of the femoral vein	+	Thrombus secondary to embolism

* Cases 5 and 6 discussed in detail in text.

LA—left atrium; PA—pulmonary artery; RV—right ventricle.

cause of progressive right ventricular failure associated with signs of peripheral venous thrombosis. The pulmonary systolic murmur and normal pulmonary component of the second heart sound suggested obstruction to the pulmonary arteries near the pulmonary valve, rather than in the small branches, when signs of pulmonary hypertension might have been expected. Virtual disappearance of pulmonary artery pulsation in case 1, strongly favored the main branches as the site of obstruction. Progressive diminution in pulsation has been noted in cases of atrial septal defect with thrombosis of the main pulmonary arteries by Canada and co-workers.[9] In case 1, the original finding of marked pulsation of the main pulmonary arteries, after signs of cardiac failure had appeared, suggests that retrograde thrombosis may have followed multiple emboli in the small branches.

The remaining 2 cases without associated diseases (case 3 and case 4) were not seen in life by the authors, and their clinical findings are therefore very briefly summarized in table 1.

Thrombosis of the Main Pulmonary Arteries Associated with Mitral Stenosis

Mitral stenosis was the most frequent single disease associated with pulmonary artery thrombosis in the series, and was present in 6 of the total of 23 patients. Five of these 6 patients were seen during life, but the diagnosis of thrombosis of the pulmonary arteries was not made. The symptoms and signs attributable to mitral valve disease overshadowed any referable to pulmonary artery thrombosis in all except 3 patients, who, in retrospect, might have been correctly diagnosed in life. Two of these 3 patients are described in detail.

Case 5. A woman, aged 55, complained of progressive dyspnea on exertion for 11 years. More recently substernal pain on exertion, relieved by rest, was noticed, and repeated hemoptyses occurred for 4 weeks. She also had a cough with sputum. On examination she was an orthopneic woman with a malar flush. The arterial pulse was of small volume, and there was an augmented 'a' wave in the jugular venous pulse. The diffuse tapping cardiac impulse suggested right ventricular hypertrophy. The second heart sound was split with marked accentuation of the pulmonary element, and there was a very faint pulmonary diastolic murmur. Triple rhythm and a soft middiastolic murmur were heard at the apex. The blood pressure was 110/60 mm. Hg. There was an effusion at the base of the right lung and slight clubbing of the fingers. The abdomen was normal and there was no peripheral edema.

The hemoglobin was 99 per cent, the white cell count was 18,000, and the platelet count was 350,000/ml.

Fluoroscopy and roentgenogram of the chest (fig. 6) showed enlargement of the right ventricle. The main pulmonary arteries were grossly enlarged and pulsating slightly. The right main branch was irregular in contour. The left atrium was enlarged, and there was a right pleural effusion. There was a rounded shadow in the right lower midzone. An electrocardiogram showed right ventricular hypertrophy.

On cardiac catheterization, the right ventricular pressure was 70/10 mm. Hg and the pulmonary artery pressure was 74/52 mm. Hg. The cardiac output was 2 L./min. An angiocardiogram showed a large right ventricle and very large pulmonary arteries. No shunt was visualized. The shadow in the right midzone appeared to become denser, suggesting pulmonary artery origin. There was poor contrast and poor filling of the distal pulmonary arteries.

The clinical course was marked by repeated pulmonary infarcts and increasing cardiac failure. The patient improved sufficiently to be discharged from hospital, but was readmitted in acute circulatory failure, with an impalpable pulse, high venous pressure, and rapid atrial fibrillation; death occurred within 24 hours.

The clinical diagnosis was pulmonary hypertension, probably due to mitral stenosis.

At autopsy there was tight mitral stenosis. The distal half of the main pulmonary artery contained laminated antemortem thrombus extending down the right and left main branches. No thrombosis was found in the femoral or abdominal veins. There were multiple pulmonary infarcts.

On histologic examination, in both main pulmonary arteries, the thrombus lay over severe atheromas and was deposited in successive layers, the deepest being well organized. It was thought to be a thrombus in situ.

In this patient the flow through the mitral valve must have been so reduced as to prevent almost completely the production of the typical murmurs. The low cardiac output would favor stasis and thrombosis in the pulmonary arteries, especially in the presence of local disease and severe pulmonary hypertension. Poor pulsation of the main pulmonary arteries is unusual with severe pulmonary hypertension; if this had been associated with the abnormal contour of the right main pulmonary artery and signs of repeated pulmonary infarcts, the correct diagnosis might have been made.

Case 6. A woman, aged 27 years, complained of dyspnea on exertion for 7 years; 3 weeks before admission the dyspnea increased and was accompanied by peripheral edema and cough with purulent sputum. There were several attacks of acute dyspnea and syncope. On examination there were signs of mitral stenosis, with right ventricular hypertrophy. The pulmonary component of the second heart sound was accentuated. The jugular venous pressure was 4 to 5 cm. above the sternal angle. An early diastolic murmur of either pulmonary or aortic incompetence

FIG. 6. *Case 5.* Posteroanterior roentgenogram of the chest showing enlargement of the right ventricle and enormous distention of the main and left main pulmonary arteries. The right main pulmonary artery is also greatly enlarged, and its contour is irregular. There is a large effusion in the right costophrenic angle, overlying a pulmonary infarct.

and a fourth heart sound were heard. The pulse was regular and of normal volume, and the blood pressure was 120/65 mm. Hg. There were peripheral edema and hepatomegaly. Bronchial breathing was audible at the base of the right lung, and scattered rales were heard throughout both lungs. Roentgenogram of the chest and fluoroscopy showed a lack of marked pulsation of the main pulmonary arteries. There was enlargement of the right atrium and ventricle, pulmonary artery, and left atrium. An electrocardiogram showed right ventricular and atrial hypertrophy, with first degree atrioventricular block.

There was steady deterioration and death in congestive heart failure.

At autopsy there was mitral stenosis and aortic incompetence, with a thrombus in the right atrium. The right ventricle was hypertrophied. The lungs showed edema, bronchitis, and pulmonary infarcts. There was adherent thrombus in the right main pulmonary artery. The smaller arteries showed hyperplasia of the internal elastic lamina, fibrinoid necrosis, acute arteritis, and local thrombosis (fig. 7). There was no source for emboli other than possibly the right atrium and the lesion was considered to be a thrombus in situ in the pulmonary artery, overlying severe vascular disease.

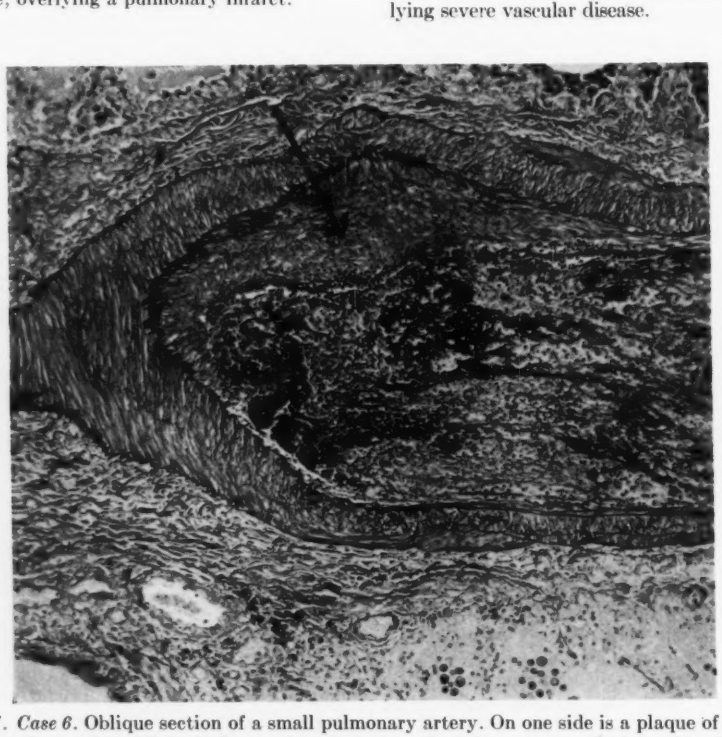

FIG. 7. *Case 6.* Oblique section of a small pulmonary artery. On one side is a plaque of atheroma (arrow), and over this, filling the lumen, is antemortem thrombus, apparently formed in situ. (× 90. Weigert's elastic stain and van Giesen's stain.)

The rapidly progressive deterioration and congestive heart failure, coupled with the episodes of acute dyspnea and fainting, in this case might have suggested the diagnosis.

The details of the other cases of mitral stenosis are outlined in table 2 (cases 7–10). The signs of thrombosis of the pulmonary arteries were obscured in case 7, 9, and 10, by other complications of the mitral valve disease, but might have been suspected in case 8, since there were episodes suggestive of repeated pulmonary infarction.

Four of the 6 patients with mitral stenosis had apparently developed a primary thrombosis in situ, and this aspect of pulmonary artery thrombosis is considered later.

Over-All Findings

Thrombosis of the Main Pulmonary Arteries in Association with Other Diseases

These cases are outlined in table 3. With the exception of patients no. 20 and 22, who were seen in life, the remainder were studied only retrospectively from case notes and autopsy reports. In many patients any signs or symptoms attributable to pulmonary artery thrombosis were completely overshadowed by some other clinical catastrophe, such as a cerebral vascular accident.

Clinical Picture

Symptoms. The commonest was dyspnea; symptoms compatible with pulmonary infarction (pleural pain or hemoptysis) were present in 11 of the 23 patients. Fainting was a striking symptom in 3 cases. In most cases, however, the symptoms of the associated or underlying disease overshadowed any due to the pulmonary lesion itself. Several patients died in coma; while in the group with mitral disease, many of the symptoms could be accounted for by the valvular lesion.

Physical Signs. The commonest sign was hypertrophy of the right ventricle, but in a number of these patients it was due to mitral stenosis. The same was true of accentuation of the pulmonary element of the second heart sound and of abnormalities in the central venous pulse. Two patients had a systolic murmur in the pulmonary area, and neither had any cardiac lesion other than right ventricular hypertrophy. The diagnostic value of the pulmonary systolic murmur and normal second heart sound in these patients is discussed later. The arterial pulse was small in volume in 5 patients, 1 of whom had mitral disease. Congestive cardiac failure was noted in 10 patients, but there were signs suggesting peripheral venous thrombosis in only 3, while 4 patients had no signs referable to disease of the heart or lungs.

Mode of Death. This was gradual in 18 and sudden in 5.

Radiology. Adequate chest films were available in 14 patients. Right ventricular and pulmonary artery enlargement was a constant feature and the lung fields appeared underfilled in 3 patients, (1 of whom, however, had pulmonary atresia). Restricted pulsation of the main arteries was striking in 2 patients, but in many cases fluoroscopy was not possible. In 1 patient with mitral stenosis (case 5), an irregular enlargement of the right pulmonary artery due to the thrombus partly obscured by a large pleural effusion was seen (fig. 6).

The important radiologic signs were underfilled lung fields and enlarged, poorly pulsating main pulmonary arteries.

Electrocardiography. Recent, adequate electrocardiograms were available in 12 patients: 8 showed right ventricular hypertrophy (4 gross and 4 moderate), and 4 showed right atrial hypertrophy. There was no evidence of enlargement of the right heart in 4 patients.

Pathologic Findings in Twenty-three Cases of Massive Thrombosis of the Large Pulmonary Arteries

Thrombosis was considered to be secondary to embolism in the majority of the cases, but appeared to have arisen in situ in a minority.

In making this differentiation we have relied mainly on the naked-eye appearances of the dissected specimen, supplemented by the histologic appearances. One source of error that we cannot exclude is the initiation of thrombosis by a small, undetected embolus. Since we are concerned here with thrombosis in the large pulmonary arteries where only massive emboli are likely to lodge, we believe that this source of error is not great.

Table 4 sets out the criteria we have used in the differentiation of primary from secondary

TABLE 3.—*Thrombosis of the Large Pulmonary Arteries Associated with Other Disease*

No.	Sex age	Associated disease	History	Clinical picture	X ray	Electrocardiogram	Autopsy findings		
							Description	Infarct	Comment
11 HD	F 72	Chronic bronchitis; aortic stenosis	Cough and dyspnea many years; hemoptysis; progressive congestive heart failure	Edema; signs of aortic stenosis; consolidation right base	LV +; fibrosis right lung		Aortic stenosis; thrombosis of main PA's; thrombosis of thigh veins	+	Impossible to tell nature of clot in PA
12 SOL	F 66	Syphilitic aortitis; coronary artery disease	1 year vertigo and syncope; intractable vomiting; sudden death	Cyanosis; small pulse; JVP + 2 cm.; heart sounds faint	—	—	Thrombosis at bifurcation of PA; syphilitic aortitis; coronary artery atheroma; no source for embolus found	0	Impossible to tell origin of clot; terminal incident suggests embolus
13 JK	M 48	Diaphragmatic hernia	Dyspnea on exertion; epigastric pain; vomiting	Severe anemia due to bleeding from gastrointestinal tract; heart and lungs normal; BP 110/85; became dyspneic and cyanosed after repair of hernia; died fairly rapidly	LV +	—	Thrombosis of main PA; branches of 1st and 2nd divisions had fibrous cords around them and many were occluded by old fibrosis; no source for embolus found	0	Impossible to tell origin in a scarred lesion; terminal incident suggests embolus; possibly previous thrombosis
14 EJ	F 83	Chronic bronchitis; cerebral thrombosis or embolus	Admitted in coma; no previous history except "dizziness"	Left hemiplegia; atrial fibrillation; BP 130/70; died in coma	—	—	Thrombosis main PA; cerebral thrombosis; lobar pneumonia; no source for embolus found	0	Impossible to tell
15 ER	F 74	Ca of bronchus; diverticulitis	Cough; hemoptysis; dyspnea; gradual deterioration; diarrhea; died slowly	Collapse left lower lobe, no cardiac lesion; JVP not raised	Collapse LLL	Nothing definite	Ca of bronchus LLL; thrombosis right main PA; no source for emboli	0	Impossible to tell origin of thrombus
16 AR	F 60	Ca of pancreas	Abdominal pain; jaundice; laparotomy disclosed Ca of pancreas	Abdominal mass; jaundice; heart and lungs normal	—	—	Ca of pancreas; thrombosis right main PA; no source for emboli found	+	Impossible to tell; history suggests thrombosis

17 WF	M 58	Ca of stomach	Died 6 days after gastrojejunostomy	Mass in abdomen; heart and lungs normal; deteriorated steadily after operation	—	—	Thrombosis right and left PA's; no source for emboli; Ca. ventriculi with secondary deposits; histology shows small PA full of organizing clot; fibrin layers could have been formed locally	+	Possible thrombosis
18 MM	F 75	Ca of bronchus; SVC thrombosis	Loss of weight; cough; swelling of face	Cyanosis of head and neck; edema of arms; JVP raised; fluid left base; heart sounds normal; died slowly after deep x-ray therapy	Left pleural effusion	—	Ca of bronchus; SVC thrombosis; thrombosis right PA; mass of ante mortem thrombus beginning at the hilum and extending into all main branches	+	Could be emboli or thrombosis; source for embolism in SVC
19 SP	F 60	Myxedema; myocardial infarction; Kimmelstiel-Wilson's disease	Dyspnea on exertion; chest pain due to previous cardiac infarct	Myxedematous; edema; raised JVP; BP 160/90; dullness at bases of lungs; faint heart sounds, no murmurs; died in diabetic coma	—	Posterior cardiac infarct ? low potass. state	Myocardial infarct; pyelonephritis; thrombosis right PA; peripheral veins not examined	+	Impossible to tell whether previous thrombosis or embolism
20 GS	M 54	Intestinal obstruction; uremia; pyelonephritis	Abdominal pain and vomiting; operation for intestinal hernia; subsequent hematuria, hemoptysis, dyspnea; died in coma	Postoperatively: cyanosed, dyspneic, signs of consolidation at right base. B.P. 100/70	Opacity at right base	—	Thrombosis of right main pulmonary artery; old thrombus in the main PA propagated clot to lower lobe; upper & middle lobes showed edema; lower lobe infarcted; histology shows organized clot with fibroblasts, sinusoids, trace of collagen; no source for emboli in leg veins	+	Almost certainly thrombosis in situ
21 DH	M 8 mo.	Pul. atresia; cerebral venous thrombosis	Cyanosed since birth; frequent bronchitis; developed diarrhea, fever, left hemiparesis with papilledema; died in coma	Marked cyanosis, dextrocardia; no murmurs; R.V. +; terminal signs of l. hemiparesis, raised intracranial pressure; polycythemia, congestive heart failure	Globular ht; no PA seen; lungs underfilled; dextrocardia; viscera normally placed	R.V. + Dextrocardia	VSD; atresia of PA distal to main branches; bronchial vessels hyperplastic; thrombus in main PA; aorta, left common carotid and renal arteries; thrombosis of longitudinal and left lateral sinus	0	Clearly thrombosis in situ in a stagnant vascular channel in a polycythemic infant

TABLE 3.—*Continued*

No.	Sex	Associated disease	History	Clinical picture	X-ray	Electrocardiogram	Autopsy findings		
							Description	Infarct	Comment
22 MI 2	M	Acute gastroenteritis	Malaise, restlessness, thirst 4 days; brought in dead	—	—	—	Recent thrombus in PA to RLL; vessels normal	0	Presumably thrombosis in situ in marasmic infant
23	M	Ca of lung; chronic bronchitis, emphysema; cor pulmonale	Progressive cough, dyspnea and loss of weight; 4 weeks before death, pain in left calf; syncopal attacks; right pleural pain; hemoptysis, dyspnea	Cyanosed; congestive r. ventricular failure	Opacity right upper zone; enlarged PA's and RV; diffuse mottling both lungs	RV ++ RA +	Ca of upper lobe of right lung. RV and RA enlarged; adherent clot in main branches of PA; source of embolus not looked for; (limited autopsy)	+	Thrombosis secondary toembolus

Ca—carcinoma; JVP—jugular venous pressure; LLL—left lower lobe; LV—left ventricle; RA—right atrium; RLL—right lower lobe; RV—right ventricle; SVC—superior vena cava; VSD—ventricular septal defect.

th ombosis. A source for an embolism in pe ipheral veins is of only limited value in the di ferential diagnosis, since it may sometimes be difficult or impossible to find in manifest ca es of embolism.[6]

Using these criteria, we consider that 7 of th 23 cases had an initial pulmonary thrombosis in situ, 6 had definite initial pulmonary emboli, and in 10 the nature of the initial incident was uncertain. It seems highly probable that these last were in reality due to emboli. Five of the 7 cases with primary thrombosis had pulmonary arterial disease or other local pathology. The histologic differences between primary embolism and thrombosis are shown in figures 8 and 9. No single 1 of the above criteria, however, is alone decisive in differential diagnosis, and figure 10 illustrates this point. In this case the lamination of the thrombus implies that the upper layers have been deposited locally, but the lack of local arterial disease and the presence of a source for emboli in the femoral veins suggest that the thrombus probably originated from an embolus.

TABLE 4.—*Criteria for the Differentiation of Primary and Secondary Thrombosis*

Primary Thrombosis	Secondary Thrombosis
Local disease of pulmonary artery.	No local disease present.
Thrombus is a cast of the vessel.	The embolus is usually coiled.
There is often deposition in episodes producing lamination of the clot in layers roughly parallel to the arterial wall. (No source for the embolus can be found).	The source of the embolus is often found and corresponds to the shape of the clot in the pulmonary artery.

Pulmonary Infarction. This was frequent, but not invariable, and occurred in 4 of the

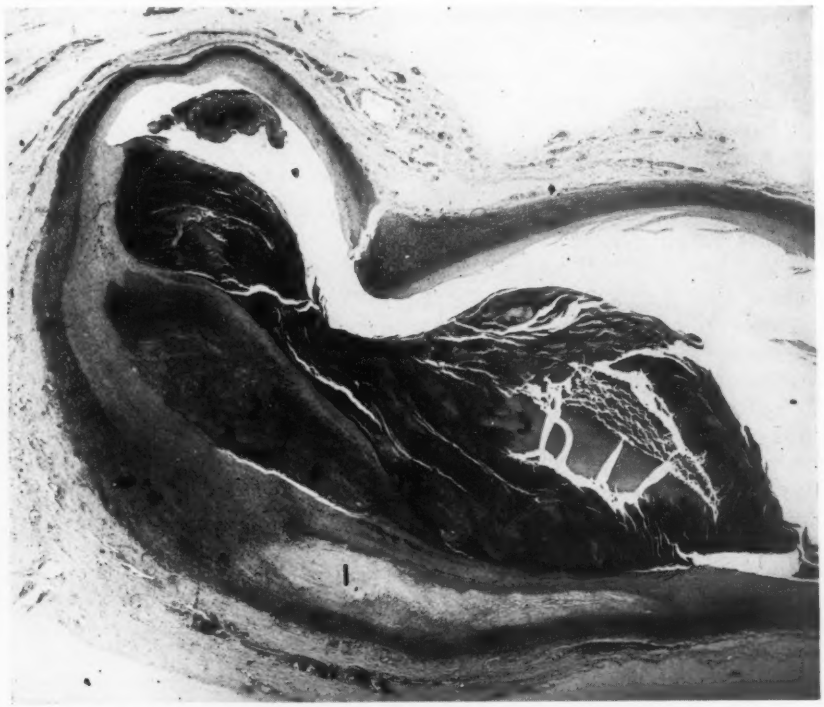

FIG. 8. *Case 7.* Section at bifurcation of lower lobe pulmonary artery. There is a plaque of atheroma on the lower side of the artery, *1*, covered by a layer of partly organized thrombus, *2*. This in turn is covered by a layer of more recent thrombus, *3*. (× 9. Hematoxylin and eosin stain.)

7 cases with primary thrombosis and in 10 of the 16 remaining cases, in which the thrombus was certainly or probably secondary to embolism.

FIG. 9. Section of a pulmonary artery branch containing an embolus that appears as 2 separate pieces. Note the absence of arterial disease. (× 9. Hematoxylin and eosin stain.)

DISCUSSION

Our cases confirm the reports in the literature that thrombotic occlusion of the main pulmonary arteries may occur as a complication of a number of diseases, especially of the heart and lungs, and to a lesser extent, of the gastrointestinal tract, but may occasionally be unassociated with any other disease. It is clear that the occlusion may develop gradually, although it may be very difficult to determine the exact age of the thrombus.

Symptoms. The symptoms of thrombotic occlusion are insidious, and in general are those of right heart failure and low cardiac output. In Middleton's[7] 53 cases, dyspnea was present in 90 per cent, hemoptysis in 62 per cent, apprehension in 30 per cent, cough in 24 per cent, and substernal pain in 24 per cent. Savacool and Charr[5] listed the principal symptoms in their own 12 cases as dyspnea, pain in the chest or epigastrium, and mental confusion. The last symptom was striking, and presumably due to cerebral ischemia. Brenner[6] stressed dyspnea as a constant feature in his cases of thrombosis of the main pulmonary

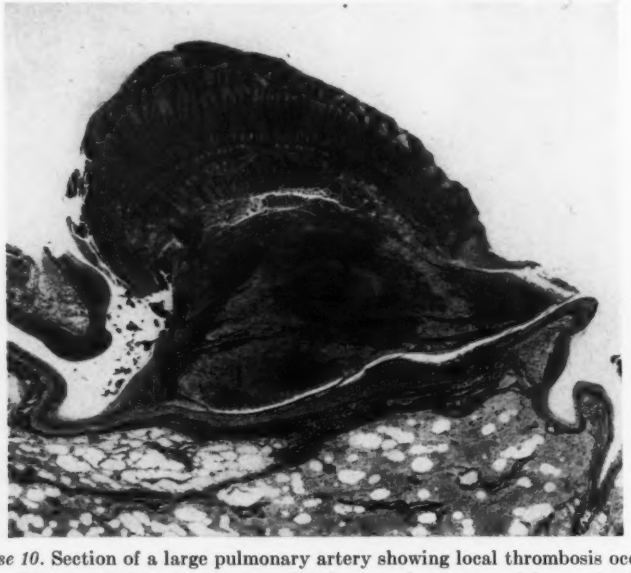

FIG. 10. *Case 10.* Section of a large pulmonary artery showing local thrombosis occurring in episodes. The first 3 layers of thrombus (1, 2, and 3) have undergone partial organization from their edges, as can be seen by the dark lines of fibrous tissue growing in toward the middle. The topmost layer of recent thrombosis shows Zahn's lines. Note the absence of disease of the underlying arterial wall. (× 5.5. Weigert's elastic and Van Giesen's stains.)

artery. Carroll[10] mentioned dyspnea in all his 5 cases and syncope on exertion in 1. Pleuritic pain and hemoptysis are likely to occur with infarction, but are often absent. Bryson[11] considered that half the cases had an acute onset of symptoms and thought that hemoptysis might arise from bronchopulmonary anastomoses. Substernal pain and syncope are presumably due to diminished coronary and cerebral blood flow, respectively. Abdominal pain may be caused by hepatic engorgement due to tricuspid incompetence. Sudden death has often been reported.

Our own cases showed a similar symptomatology, especially sudden dyspnea, fainting, and pulmonary infarction, although mental confusion was not a striking feature, and in several cases there were no symptoms attributable to the thrombosis. Sudden onset and sudden death were not common.

Physical Signs. Cyanosis was present in 68 per cent of Middleton's 53 cases. It is presumably peripheral in nature and is due to a low cardiac output, except when there is a right-to-left shunt, which would be intensified by the occlusion of the pulmonary arteries.[9] Signs of tricuspid incompetence, peripheral edema, hepatic engorgement, and increased jugular venous pressure, together indicating congestive failure of the right ventricle, were reported by Carroll[10] and by Hanelin and Eyler.[12] Signs of pulmonary hypertension (enlarged right ventricle and accentuated pulmonary element of the second heart sound) have also been frequently mentioned. Two of the 7 cases described by Keating and co-workers[13] had a lone apical systolic murmur, 2 had diastolic murmurs over the pulmonary artery, which in 1 was associated with an apical systolic murmur; but 3 had no murmurs at all. Carroll's[10] 5 cases all had systolic murmurs in the region of the pulmonary artery, as had Middleton's[7] case. Savacool and Charr[5] stress the small pulse, low blood pressure, and restlessness as signs of low cardiac output, but these probably do not occur until the main pulmonary arteries are substantially occluded. Gibbon and associates[14] in experimental studies on dogs, found that the systemic blood pressure did not fall until 60 per cent occlusion of more than 75 per cent of the pulmonary arteries caused death.

The physical signs in our own cases were often difficult to evaluate, since the associated or underlying disease tended to mask them. However, the 3 cases with repeated thromboembolic episodes of unknown cause presented the features of right-sided heart failure with low output, a systolic murmur over the pulmonary artery or at the apex, a normal or soft pulmonary component of the second heart sound, and enlargement of the right ventricle. Accentuation of the pulmonary component of the second heart sound suggesting pulmonary hypertension was found only in patients in whom pulmonary hypertension was present before the occurrence of the thrombosis. It is probable that a thrombus in the main pulmonary arteries extending down close to the valve could be associated with a low pressure in the pulmonary artery and, hence, a normal or soft pulmonary component of the second heart sound, which was in fact present in 2 of our patients.

Radiologic Signs. The radiologic signs have been reviewed by Hanelin and Eyler.[12] The main pulmonary arteries were enlarged, while the peripheral branches were small; the lung fields appeared clear, with the exception of shadows cast by pulmonary infarcts. Keating and associates[13] found right ventricular and pulmonary arterial enlargement and clear lung fields in all their 7 cases. Absence of pulsation of the main pulmonary arteries (which had previously pulsated strongly) was noted by Canada and co-workers[9] in 1 of their 3 cases with thrombosed pulmonary arteries, but comment has not been previously made on this point. Absence of pulsation in an enlarged right main branch is unusual, and was helpful in diagnosis in 1 of our cases. But it should be remembered that enlargement of the main pulmonary artery and left main branch may be associated with poor pulsation in cases of pulmonary stenosis.

Adequate radiology in many of our cases was not possible, but in 2 patients (cases 1 and 2) a combination of clear lung fields and enlarged pulmonary arteries was seen. In a

third case (case 5) the contour of the enlarged right pulmonary artery was irregular, being quite unlike the smooth convex margin usually seen when this vessel is enlarged.

The Electrocardiogram. As might be expected, the electrocardiogram has been reported to show hypertrophy of the right ventricle, and did so in many of our patients.

Diagnosis. The diagnosis of pulmonary artery thrombosis should be considered whenever a patient presents unexplained congestive cardiac failure, dyspnea, fainting, repeated episodes of pulmonary infarction, or pain in the chest. If the clinical picture includes evidence of peripheral venous thrombosis, a systolic murmur over the pulmonary artery, and a normal or soft component of the second heart sound the diagnosis becomes more probable. If, in addition, x-ray films of the chest show enlargement of the right ventricle and pulmonary arteries (without significant pulsation of the latter) and clear lung fields or shadows suggesting infarction, together with electrocardiographic evidence of right ventricular hypertrophy, the diagnosis becomes almost certain.

Cardiac catheterization is of value in excluding other lesions, such as septal defects and pulmonary stenosis, but contributes little positive information other than confirming right ventricular hypertension. Exclusion of pulmonary stenosis may be difficult owing to the difficulty of passing the catheter into a thrombosed main pulmonary artery.

Differentiation from mitral stenosis may also be difficult, especially as pulmonary artery thrombosis may complicate this condition, and the typical murmurs may be difficult to hear in patients with severe pulmonary hypertension. The characteristic radiologic vascular changes seen in mitral disease,[15, 16] and enlargement of the left atrium, should assist in making the differential diagnosis. Absence of a history or clinical evidence of lung disease should exclude a diagnosis of chronic anoxic cor pulmonale. Differentiation from idiopathic pulmonary hypertension may be difficult, and it is possible that pulmonary artery thrombosis might complicate this condition.[3] Obscure forms of chronic pulmonary fibrosis would be likely to show characteristic radiologic changes in the lungs, which are absent in pulmonary artery thrombosis.

Angiocardiography should be the most satisfactory diagnostic method, but was not found to be of real value in case 5, while the other cases in which the condition was suspected were too ill for the investigation to be carried out. With improved and safer techniques of angiography, it might be performed if the diagnosis is suspected.

Treatment. Lack of success has probably been due to failure of early diagnosis. Prolonged anticoagulant therapy offers the only hope of preventing extension of the thrombus. If the thrombosis is secondary to repeated pulmonary emboli from thrombosis of the leg veins that cannot be controlled by anticoagulants, ligation of the inferior vena cava might have to be considered.

Genesis of the Thrombosis and Associated Disease

It is often considered that thrombosis in the pulmonary arterial tree is always secondary to embolism. Brenner[6] considered that primary thrombosis did sometimes occur, especially in association with disease of the pulmonary arteries, and our own findings of local pulmonary artery disease in 5 of 7 cases with primary thrombosis support this view. Differentiation between primary thrombosis and that secondary to embolism may be impossible, however. While a recent embolus is easy to recognize because the clot is not a cast of the artery and is usually coiled, after a few days further thrombus is deposited around it, tending to obscure the original outline. Where a clot does not fully obstruct an artery, endothelium rapidly grows over it, while organization from the arterial wall fixes it in position.[17] By contrast, a local thrombus fits the vessel and is often laid down in layers at different times. Glynn and Knowles[18] considered this lamination to be good evidence of primary thrombosis, although Brenner[6] maintained that laminated thrombi from peripheral veins may be dislodged and carried to the pulmonary artery, so that the phenomenon might be found in thrombi secondary to embolism. In our view, however, the presence of a clot laminated in planes

roughly parallel to the wall of the artery, fitting the vessel, and overlying local arterial disease is virtually diagnostic of primary thrombosis in situ.

A number of different forms of intrathoracic disease have been described in association with thrombosis of the large pulmonary arteries, particularly congenital heart disease and pulmonary tuberculosis. Mitral stenosis has not featured prominently.

Savacool and Charr[5] reported 12 cases associated with pulmonary tuberculosis. They were convinced that the thrombi arose in situ in view of their size and shape, their firm adherence to the intima, invasion by strands of connective tissue from the intima, and the deposition of fibrin platelets and other blood constituents. The primary site of thrombosis appeared to be the termination of the small branches of the main pulmonary artery, which were often embedded in fibrous tissue or tuberculous consolidation. Furthermore, they noted that the right pulmonary artery was involved more frequently than the left, which they attributed to the fact that the right pulmonary artery is compressed between the vein and bronchus and is crossed by the aortic arch, while the left pulmonary artery is relatively free. Gordon and Perla[19] described pulmonary arterial thrombosis in a child with patent ductus arteriosus, pulmonary stenosis, and subacute bacterial endocarditis, and Whipham[20] described an infant of 7 months, with patent ductus arteriosus and a thrombus in the pulmonary artery that projected through the valve into the right ventricle. Dickinson[21] described occlusion of the main trunk and both main branches of the pulmonary artery in a boy aged 4½ years who had pulmonary stenosis and a ventricular septal defect. Canada[9] reported 3 cases of atrioseptal defect with pulmonary artery thrombosis. Widespread focal thrombosis in the small pulmonary vessels has been described by Rich[22] in cases of the tetralogy of Fallot, while in 1 of our 23 cases widespread thrombosis, including the main pulmonary arteries, occurred in association with partial pulmonary atresia and a large ventricular septal defect.

Thrombosis of the large pulmonary arteries has been reported in children in the absence of congenital heart disease. Gehrt[23] found 7 cases in 600 autopsies, 5 of which followed measles. Gunter[24] described thrombosis in a pair of identical twins, one of whom died of gastroenteritis and the other after mastoidectomy. Since children rarely develop pulmonary embolism, these cases provide evidence in favor of primary thrombosis, and there was 1 such in our series.

Primary thrombosis might be expected to occur in association with disease of the pulmonary arteries, such as atherosclerosis, which may be found in chronic lung disease and in congenital and acquired heart disease. Where disease of the arterial wall is combined with a low cardiac output, a sluggish pulmonary blood flow, and enlargement of the main pulmonary arteries, thrombosis in situ is particularly favored (fig. 8).

Disease of the pulmonary arteries is an important complication of mitral valve disease where atherosclerosis may involve the large branches, as in our cases 5 and 7. Furthermore, pulmonary hypertension is common, and the cardiac output is often reduced in severe cases. The summation of these 3 factors would be conducive to primary thrombosis.

It is not surprising, therefore, that 19 of 88 cases of pulmonary artery thrombosis collected by Savacool and Charr[5] occurred in association with mitral disease, and the incidence in our series is of the same order (6 out of 23 cases). An additional case of thrombosis of the right pulmonary artery in a patient with mitral stenosis, thought to have occurred following cardiac catheterization, has recently been reported by Nightingale and Williams.[25] A further factor favoring thrombosis is the tendency to peripheral venous thrombosis and pulmonary embolism from peripheral thrombosis in mitral disease. This has recently been stressed by Wood[26] in cases with a low cardiac output and very high pulmonary vascular resistance. It is possible, however, that some of the organic occlusive lesions in the smaller arteries, which are not infrequently found in mitral stenosis, might be originally thrombotic or embolic in nature. Thrombosis of the small

pulmonary arteries, together with arteritis, was a feature in our case 6 (fig. 7).

Pulmonary Infarction in Association with Thrombosis of the Pulmonary Arteries

Pulmonary infarction is not an invariable feature in cases of thrombus of the large pulmonary arteries. Of 7 cases reported by Keating and co-workers,[13] infarcts were present in only 2, in both of which previous pulmonary emboli had occurred. Infarcts were absent in Pou and Charr's[27] 6 cases, and in 4 of Brenner's[28] cases. Fowler[29] found no infarction in a single case of thrombosis of the right and left main pulmonary arteries and explained its absence by the presence of anastomoses between the bronchial and pulmonary arteries. In this connection, the observation of Carroll[10] is of interest. At thoracotomy in 1 of his cases, the left pulmonary artery was found to be occluded, but aspiration distal to the block yielded oxygenated blood, which must have been due to retrograde bronchial flow. Gradual occlusion of the main arteries would allow time for these anastomoses to enlarge. The absence of infarction does not, however, permit distinction between primary and secondary thrombosis, since progressive thrombosis on the site of an embolus would create the same condition. A survey of the literature suggests that infarcts were more common in cases in which there was a definite source for, or history of, pulmonary embolism, than in those thought to have primary thrombosis of the pulmonary arteries.

In our own series, 14 of 23 cases had pulmonary infarcts that occurred with equal frequency in association with primary and secondary thrombosis. In 1 patient (case 5) the bronchial arteries were enlarged.

Summary

A series of 23 cases of thrombotic occlusion of the large pulmonary arteries, not due to acute massive embolism, has been presented. The clinical, radiologic, electrocardiographic, and pathologic features have been described, together with the results of special investigations in certain cases. It is concluded that thrombotic occlusion of the large pulmonary arteries can occur insidiously and present a characteristic picture of progressive right ventricular failure, the special features of which are outlined in detail. In most cases the thrombosis was secondary to embolism, but in 7 it was considered to have arisen primarily in the pulmonary artery. Six of the 23 cases had mitral stenosis, which appeared to favor primary thrombosis of the large pulmonary arteries. The etiology, diagnosis, differential diagnosis, and possible treatment have been discussed, and it is suggested that the diagnosis should be considered in any patient with obscure right ventricular failure, attacks of syncope, acute dyspnea, or chest pain; and especially if there have been episodes suggestive of pulmonary infarction. Patients with mitral stenosis who deteriorate for no apparent reason and show alteration in the second heart sound and decrease in the pulsation of the pulmonary arteries, should also be suspected of having developed a massive pulmonary artery thrombosis.

Acknowledgment

We are grateful to Dr. J. Edmunds for permission to use his notes on case 1 and to Dr. C. S. Treip for his postmortem findings. We wish to thank Professor J. McMichael for permission to publish cases 5 and 7 and Dr. J. Shillingford for his help and advice. Miss R. Klein, Mr. Knowlden, and Mr. Booker provided the photographs. The drawing was executed by Miss D. M. Baker.

Summario in Interlingua

Es presentate un serie de 23 casos de occlusion thrombotic del grande arterias pulmonar, non causate per acute embolismos massive. Es describite le aspectos clinic, radiologic, electrocardiographic, e pathologic, insimul con le resultatos de investigationes special interprendite in certe casos. Le autores conclude que occlusion thrombotic del grande arterias pulmonar pote occurrer insidiosemente e que illo presenta alora un tableau characteristic de progressive disfallimento dextero-ventricular. Le aspectos special de illo es delineate in detalio. In le majoritate del casos le thrombose esseva secundari a embolismo. In 7 casos, de altere latere, illo pareva haber occurrite primarimente in le arteria pulmonar. Sex de 2

ca os habeva stenosis mitral, lo que pareva su portar le interpretation de thrombosis pr mari in le grande arterias pulmonar. Es di cutite le etiologia, le diagnose, le diagnose di ferential, e le formas possibile de tracta- m nto. Es suggerite que le diagnose de occlu- si n thrombotic del grande arterias pulmonar de e esser prendite in consideration in omne pa iente con obscur disfallimento dextero- ve tricular, attaccos de syncope, dyspnea ac te, o dolores thoracic, specialmente in le pr sentia de un historia de episodios que sug- ge e infarcimento pulmonar. Le suspicion de u disveloppamento de massive thrombosis del grande arterias pulmonar es etiam justificate in patientes con stenosis mitral qui se deteriora sin causa apparente e qui monstra alteration in le secunde sono cardiac insimul con reduction del pulsation in le arterias pulmonar.

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Graphic Registration of Cardiac Thrills in Acquired and Congenital Heart Disease

By David C. Levinson, M.D., John P. Meehan, Jr., M.D., Leonard H. Schwartz, M.D., and George C. Griffith, M.D.

A method is described for the graphic registration of cardiac thrills. A thrill is defined as a chest wall vibration of sufficient intensity to be recognized by tactile sensation.

CARDIAC thrills were picked up through a pulse capsule attachment and recorded on a Sanborn Twinbeam Cardiette. Simultaneously, heart sounds and murmurs were recorded on a second channel. The relative sensitivity of the 2 systems (stethoscopic microphone and amplifier, and pulse capsule pickup and amplifier) was determined by comparison with a calibrated audio signal. The pulse capsule attachment had its greatest sensitivity at 80 cycles per second, at which point it was 6½ times as sensitive as the stethoscopic microphone. The pulse capsule attachment was relatively insensitive below 20 and above 120 c.p.s. The stethoscopic microphone was uniformly sensitive from 20 to above 250 c.p.s.

Thrills were recorded in a large number of patients with acquired and congenital heart disease, and were within the range of 60 to 100 c.p.s., with the greatest number falling in the range of 75 to 85 c.p.s.

This technic affords the clinician a new method of visually recording a palpable clinical finding. In addition to its value as a teaching aid, the record indicates the time and duration of the thrill in the cardiac cycle, and provides a permanent record of this physical finding.

The purposes of this report are to describe a method that has been used for the graphic registration of cardiac thrills and to present data concerning the frequencies of cardiac thrills in several clinical disorders. By definition, a thrill is a vibration of the chest wall of sufficient intensity to be recognized by tactile sensation. These vibrations are usually produced by rapid blood flow through a narrowed orifice into a larger chamber or vessel. Although thrills can be recognized over a large range of frequencies, vibrations in the lower frequency range are most readily appreciated.[1] Partly for this reason, palpable thrills are all of fairly low frequency. For these reasons, a method for recording the low-frequency vibrations of the chest wall was developed, based on the use of a pulse capsule attachment.* As will be shown later, this method of recording the vibrations of the chest wall gives some frequency discrimination in that frequencies much over 100 c.p.s. are fairly well rejected by this recording system.

Methods and Equipment

A Sanborn Twinbeam Model no. 62 Cardiette was used to obtain simultaneous records of heart sounds and cardiac thrills. In the upper channel, the cardiac sounds were recorded with the conventional stethoscopic microphone and heart sound amplifier. In the lower channel, records of the low-frequency vibrations of the chest wall were obtained. This included the thrill, heart sounds, and slow movements of the chest wall such as ventricular lifts. In brief, the latter pulse capsule attachment produced a record somewhat similar to an apex cardiogram, but in addition registered cardiac thrills.

The relative sensitivity of the 2 recording systems was determined by comparing their performance with a calibrated audio signal. The standardized audio signal was obtained by amplifying the output of a Hewlett-Packard type 140A oscillator to drive a specially constructed speaker unit. The microphone and pulse capsule attachment were similarly oriented in front of the speaker.

From the Cardio-Pulmonary Laboratory of the Cedars of Lebanon Hospital, Los Angeles, and the Division of Cardiology, Department of Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

* Pulse capsule attachment provided for use with a Sanborn Model No. 2 Cardiette.

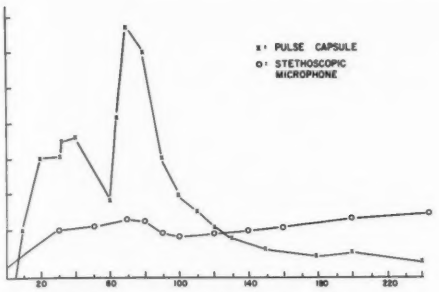

FIG. 1. Relative sensitivity (ordinate) of the 2 recording systems: stethoscopic microphone with heart sound amplifier and pulse capsule pickup with general purpose amplifier. Abscissa, cycles per second.

Outputs of both systems were measured as the amplitudes of the respective galvanometer traces of the Sanborn twinbeam recorder. The audio output from the speaker was examined by means of a linear microphone and cathode-ray oscilloscope. The experimental data from both systems under test were corrected for the nonlinear characteristics of the speaker used in the calibration studies. The relative sensitivities of the 2 systems at different frequencies are shown in figure 1. At 70 c.p.s. the pulse capsule attachment was about 4 times as sensitive as the stethoscopic microphone and at 80 c.p.s. it was approximately 6½ times as sensitive.

RESULTS

Simultaneous records of the heart sounds and thrills were obtained in 75 patients with acquired and congenital heart disease and palpable thrills. The following 10 representative cases are presented. The diagnosis was made in all instances after extensive clinical and laboratory study with confirmation by cardiac catheterization in most instances.

Acquired Heart Disease

Case 1: "Pure" Mitral Stenosis (fig. 2). Heart sounds and thrill were recorded simultaneously from the mitral area. The frequency of the diastolic thrill was 85 c.p.s. The murmur was maximum in middiastole, whereas the thrill persisted throughout diastole.

Case 2: "Pure" Mitral Insufficiency (fig. 3). Heart sounds and thrill were recorded simultaneously at the mitral area. The systolic thrill had a frequency of 75 c.p.s., was pansystolic, and was of uniform intensity. The murmur was also pansystolic but had a complex wave form containing components of both high and low frequency.

Case 3: "Pure" Aortic Stenosis (fig. 4). Heart sounds and thrill were recorded simultaneously at the primary aortic area. The frequency of the systolic thrill was 65 c.p.s. Both thrill and murmur were of maximum intensity in midsystole.

Case 4: Aortic Insufficiency and Stenosis, Probable Eventration of Aortic Valve Cusp (fig. 5). Heart sounds and thrill were recorded simultaneously at the secondary aortic area. The frequency of the diastolic thrill was 100 c.p.s., and the murmur at its maximum ampli-

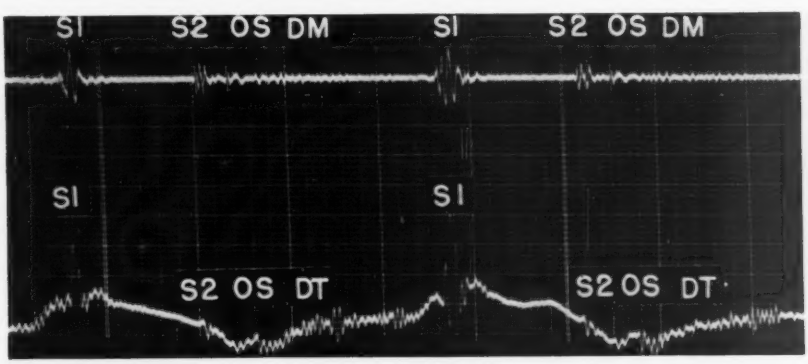

FIG. 2. Heart sounds and thrill in "pure" mitral stenosis. *S1*—first heart sound; *S2*—second heart sound; *S3*—third heart sound; *OS*—opening snap of mitral valve; *ST*—systolic thrill; *DT*—diastolic thrill; *A*—closure of aortic valves; *P*—closure of pulmonic valves. (The same abbreviations are used in all subsequent records.)

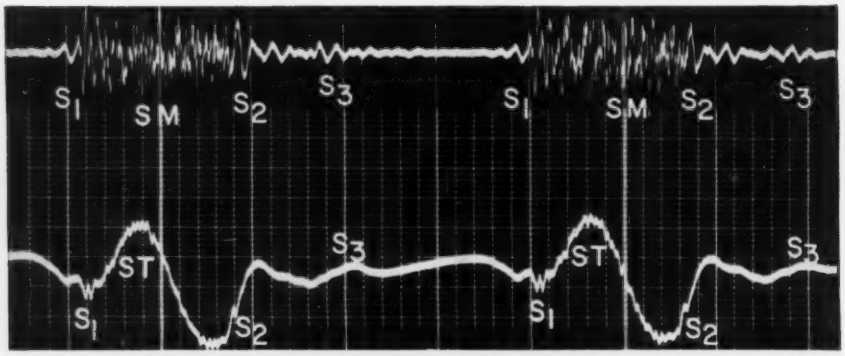

FIG. 3. "Pure" mitral insufficiency

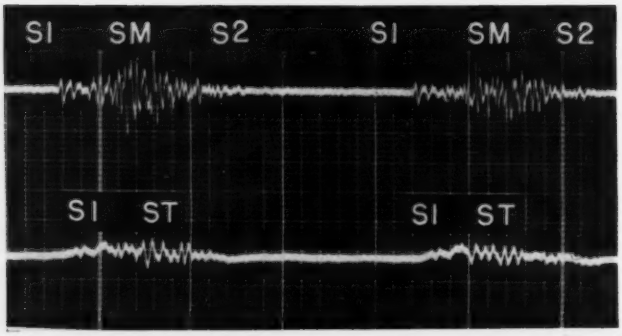

FIG. 4. "Pure" aortic stenosis

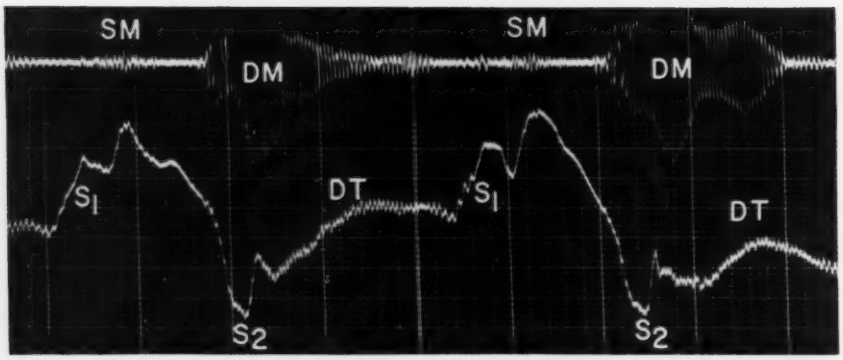

FIG. 5. Aortic insufficiency and stenosis

tude was 150 c.p.s. The thrill was of uniform intensity and pandiastolic in duration, whereas the murmur was loudest in early diastole.

Case 5: Tricuspid Insufficiency (*fig. 6*). Heart sounds and thrill were recorded at the tricuspid area. The frequency of the systolic thrill was 85 c.p.s. Both thrill and murmur were pansystolic in duration.

Congenital Heart Disease

Case 6: Atrial Septal Defect (*fig. 7*). Heart sounds and thrills were recorded at the pulmonic area. The frequency of the systolic thrill was 75 c.p.s. Both thrill and murmur were pansystolic in duration.

Case 7: Interventricular Septal Defect (*fig. 8*).

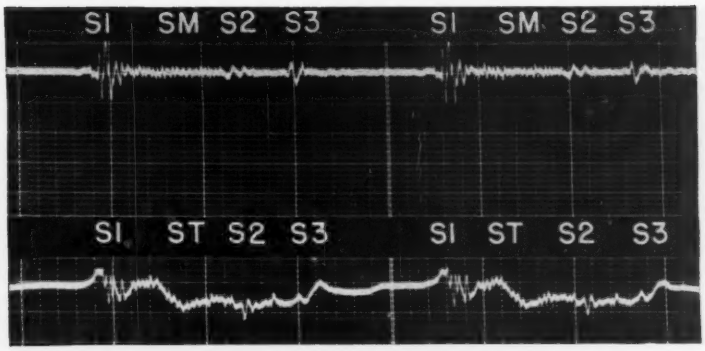

FIG. 6. Tricuspid insufficiency

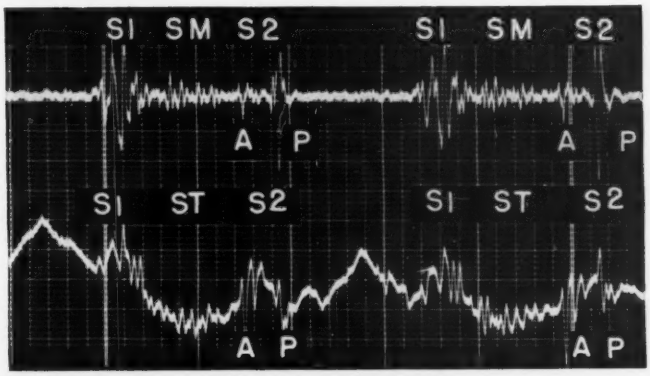

FIG. 7. Atrial septal defect

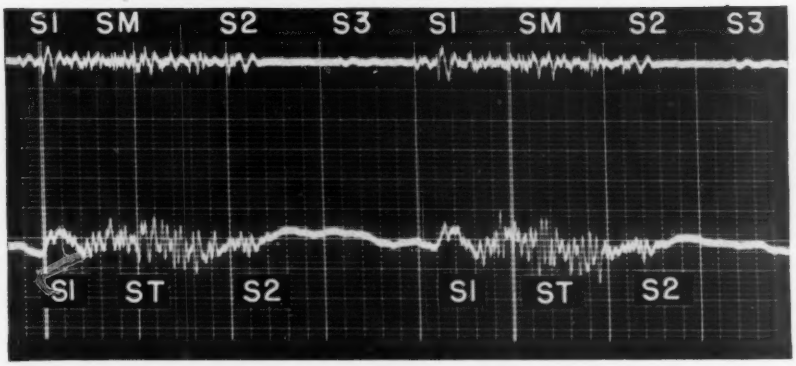

FIG. 8. Interventricular septal defect

Heart sounds and thrill were recorded at the secondary aortic area. The frequency of the systolic thrill was 90 c.p.s. Both thrill and murmur were pansystolic. The thrill reached its peak intensity in midsystole.

Case 8: Patent Ductus Arteriosus with Pulmonary Hypertension and Reversal of Shunt (*fig. 9*). Heart sounds and thrill were recorded at the pulmonic area. The frequency of the diastolic thrill was 75 c.p.s. Both thrill and murmur were pandiastolic in duration.

Case 9: Pulmonic Valvular Stenosis (*fig. 10*).

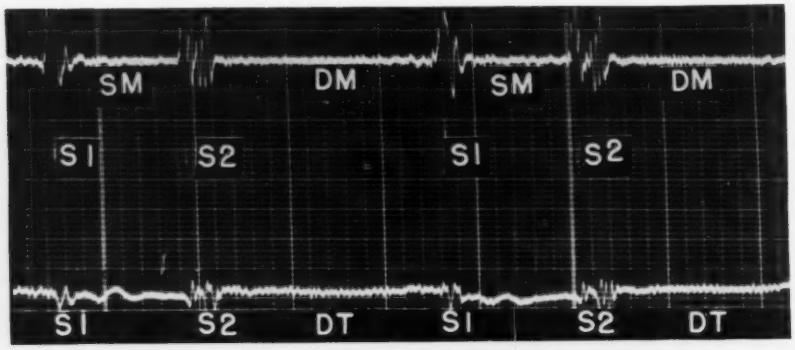

FIG. 9. Patent ductus arteriosus with pulmonary hypertension

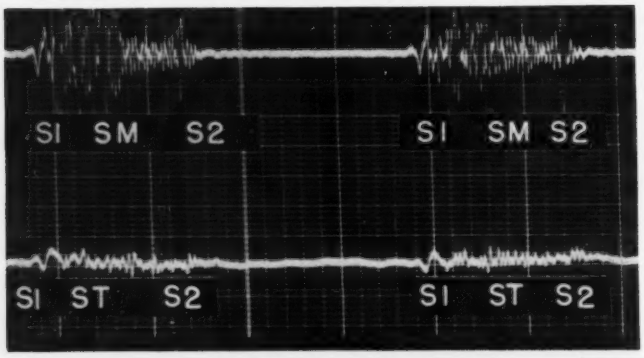

FIG. 10. Pulmonic valvular stenosis

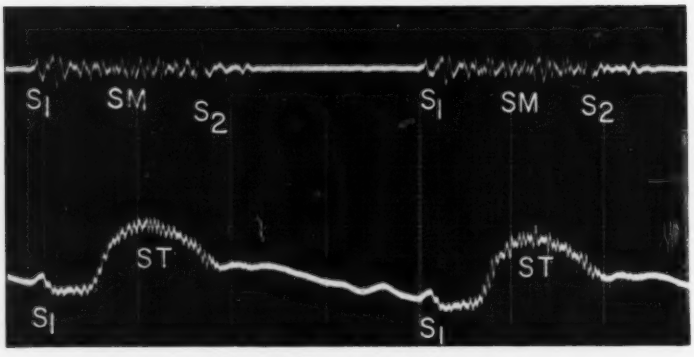

FIG. 11. Truncus arteriosus

Heart sounds and thrill were recorded at the pulmonic area. The frequency of the systolic thrill was 70 c.p.s. Both thrill and murmur were pansystolic. The murmur was loudest in early systole whereas the thrill appeared more uniform throughout systole.

Case 10: Truncus Arteriosus (*fig. 11*). Heart sounds and thrill were recorded at the primary aortic area. The frequency of the systolic thrill was 85 c.p.s. Both murmur and thrill were pansystolic.

In the 10 cases most of the thrills were in the range of 60 to 100 c.p.s., with the greatest number falling in the range of 75 to 85 c.p.s.

Vibrations of the chest wall that can be recorded have a wide frequency range. Vi-

TABLE 1. *Precordial Vibrations*

Phenomenon	Frequency range of vibrations (c.p.s.)	Physical method
G neral movements of hest wall	0–5	Palpation
D stolic sound (third nd fourth heart ounds)	5–50	Palpation and auscultation
F st and second heart ounds	10–100	Auscultation and palpation
V vular snap, diasto- ic rumble at apex	10–150	Auscultation and palpation
Sy stolic murmurs, distolic basal mur- murs	150–1000	Auscultation

sada[2] has tabulated the type and range of these vibrations and classified them according to the nature of the vibrations and as to whether they are best recognized by palpation or auscultation (table 1).

The palpable vibrations heretofore described are listed in the table as being in the range of 0 to 150 c.p.s. These vibrations consist of slow movements of the chest wall, heart sounds, and the diastolic rumble of mitral stenosis. If the diastolic rumble of mitral stenosis is eliminated, these palpable vibrations range from 0 to 100 c.p.s. Also, heart sounds at times may be detected by both auscultation and palpation. Finally, it is to be noted that systolic murmurs and diastolic basal murmurs have a frequency range beginning at 150 c.p.s. and ranging upward to 1000 c.p.s.

The pulse capsule attachment used to record cardiac thrills was found to have its greatest sensitivity at 80 c.p.s. The range of most cardiac thrills that were recorded was between 75 and 85 c.p.s. Vibrations of this frequency are palpable if they are of sufficient intensity and duration.

The ability to record a thrill permits the clinician to confirm and have a permanent record of this physical finding. The record indicates the timing of the thrill within the cardiac cycle as well as its absolute duration. With this technic, a new teaching aid is added to the armamentarium of the clinician.

SUMMARY

A technic for the graphic registration of cardiac thrills and other low frequency vibrations of the chest wall has been described. Palpable cardiac thrills were noted to have a frequency range between 60 to 100 c.p.s., with the greatest number in the range of 75 to 85 c.p.s.

SUMMARIO IN INTERLINGUA

Es describite un technica pro le registration graphic de fremitos cardiac e de altere vibrationes a basse frequentias in le pariete thoracic. Esseva notate que palpabile fremitos cardiac ha un scala de frequentias de inter 60 e 100 cyclos per secunda. Le plus grande numero de illos occurre con frequentias de inter 75 e 85 cyclos per secunda.

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Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly wherever and to whatever abysses Nature leads, or you shall learn nothing. I have only begun to learn content and peace of mind since I have resolved at all risks to do this.—HUXLEY.

Serum Glutamic-Oxalacetic Transaminase in Coronary Artery Disease

A Review of 201 Cases

By Bernard H. Ostrow, M.D., Daniel Steinberg, M.D., Howard E. Ticktin, M.D., George N. Polis, M.D., and John M. Evans, M.D.

The results of serial glutamic-oxalacetic transaminase (GOT) assays in 201 cases in which coronary artery disease was suspected are correlated with the clinical, laboratory, and electrocardiographic changes. In 95 per cent of the cases diagnosed as myocardial infarction on the basis of clinical and electrocardiographic evidence there was an elevation of serum GOT. On the other hand, in 12 per cent of the cases in which clinical and electrocardiographic findings were negative or equivocal with regard to myocardial infarction, there was an elevated serum GOT. In 18 cases that were autopsied the correlation between acute myocardial necrosis and serum GOT elevation was 100 per cent.

WHILE the diagnosis of acute myocardial infarction can in most instances be established by a correlation of clinical, laboratory, and electrocardiographic evidence, there is nevertheless a significant number of cases in which an unequivocal diagnosis is not possible. The elevation of serum levels of glutamic-oxalacetic transaminase (GOT) following myocardial infarction, reported first by LaDue, Wroblewski, and Karmen,[1] and since amply confirmed in a number of laboratories,[2-9] appears to offer a new objective test for establishing this diagnosis.

We have previously found, in cases of transmural myocardial infarction with clear-cut electrocardiographic evidence of myocardial necrosis, that the correlation between the electrocardiographic diagnosis and the elevation of glutamic-oxalacetic transaminase is better than 90 per cent.[2-4] The present report describes our results in a series of 201 cases in which coronary artery disease was considered in the differential diagnosis and attempts an evaluation of the clinical application of this new diagnostic tool.

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This work was supported in part by a grant-in-aid of the Washington Heart Association and a grant from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

Methods and Material

In this series were included 201 patients with clinical or electrocardiographic evidence suggesting coronary artery disease at the time of hospitalization, although the final diagnosis not infrequently absolved the coronary arteries. Blood samples were drawn for transaminase assay on at least 5 successive days after the onset of symptoms. In most patients serial electrocardiograms, erythrocyte sedimentation rates, and white blood cell counts were determined daily and rectal temperatures recorded every 4 hours during the first few days. All patients were seen and in most cases observed closely by 1 of the authors during their hospital stay.

At the conclusion of the study each clinical record was reviewed without knowledge of the transaminase levels. All cases were listed as positive or negative for acute myocardial infarction on the basis of the serial electrocardiograms, the history, white blood cell counts, erythrocyte sedimentation rates, body temperature, and the clinical course, with particular reference to the development of shock, left heart failure, and paroxysmal arrhythmias. Each case was assigned to 1 of the following groups on the basis of the electrocardiogram:

Group I. Acute Transmural Myocardial Infarction. Characterized by the development of Q-waves of 0.04 sec. or greater duration, with reciprocal ST-segment shifts and T-wave inversions.

Group II. Normal Electrocardiogram.

Group III. ST-T Changes. This group included

myocardial ischemia, left ventricular hypertrophy and strain, digitalis effect, and subendocardial ischemia, defined as 2 mm. or more J-junction depression in the precordial leads.

Group IV. Masking Electrocardiograms. Due to bundle-branch block, previous infarction, Wolff-Parkinson-White syndrome, or pericarditis.

Serum GOT was determined by a modification of the method of Karmen, Wroblewski, and LaDue[10] reported in detail elsewhere.[11] Results are expressed as units per ml. of serum. The unit is defined as that amount of enzyme that causes optical density, at a wavelength of 340 mμ, to fall at the rate of 0.001 O.D. U./min. under the conditions of the assay at 25° C., with an effective light path of 1 cm. The Beckman DU spectrophotometer was used for the greater part of this study. However, the Bausch and Lomb Spectronic 20 Colorimeter, specially modified for use in this assay, was also found to be a satisfactory instrument. Analysis of the same sample on the 2 instruments checked within ±5 per cent. For routine use, especially when a controlled temperature bath is employed, the latter instrument is more convenient but somewhat less precise.[11] Normal values ranged from 10 to 33 U./ml. serum.[2] However, myocardial necrosis was not considered unless the transaminase value was 48 U./ml. or more.

Results

Group I. Acute Transmural Myocardial Infarction

Sixty patients showed the typical electrocardiographic changes of transmural myocardial infarction. The transaminase results in these cases are presented in some detail, since the interpretation of the data in the less well defined cases depends to a large extent upon the results noted in this group.

Characteristically, there was a sharp rise in serum GOT within the first 24 hours after onset of symptoms. Peak values, ranging from 50 to 375 U./ml., were reached on the average within 26 hours, with a range of 2 to 96 hours. The return to normal was equally characteristic but not so rapid, normal values being reached in most cases by the sixth day and in all cases by the eighth day from onset. Figure 1 shows the mean and the extreme GOT levels as a function of the number of days following infarction. The mean peak was 164 U./ml. While this value in women (206 U./ml.) was somewhat higher than that in men (145 U./ml.) the difference was not statistically significant ($p > 5.0$ per cent). Even though the elevations

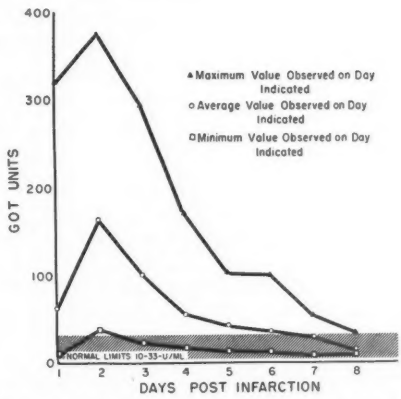

FIG. 1. Average and extreme levels of serum GOT plotted as a function of number of days after onset of myocardial infarction (ordinate).

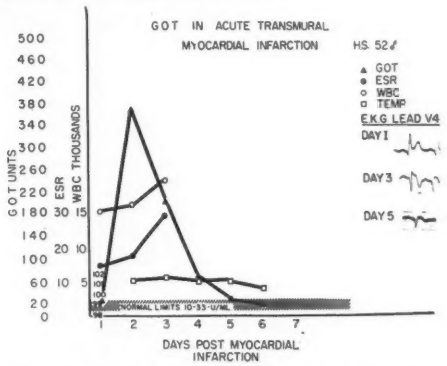

FIG. 2. Results in a typical case of transmural myocardial infarction (group I).

of enzyme persisted for 4 to 6 days in most cases, they returned to normal in some cases as early as the second or third postinfarction day. Transitory elevations of this type were more common in the group III cases discussed below.

Fifty-eight of the 60 cases in group I, all considered to have suffered myocardial infarction by our clinical criteria, showed elevation of the serum GOT, a positive correlation of 97 per cent. The following case is illustrative of the group.

H.S. (fig. 2), a 52-year-old man, without previous history of cardiovascular disease, was admitted to the hospital on April 13, 1955, following acute onset of substernal oppression and shortness of breath, which awakened him from sleep and continued until relieved by opiates. On admission the pulse was 88,

TABLE 1.—*Laboratory and Clinical Data in Sixty Cases of Acute Transmural Myocardial Infarction*

	Mean peak value	Range of peak values	Mean time in hours from onset to peak value
GOT	164 U./ml.	48–375 U./ml.	27
WBC	14,400/c. mm.	5,600–25,000/ c. mm.	46
ESR	35 mm./hour	6–58 mm./hour	96
Rectal temperature	101.3 F.	100.0–104.0 F.	36

GOT = Glutamic-oxalacetic transaminase.
WBC = White blood cell count.
ESR = Erythrocyte sedimentation rate.

there were occasional premature ventricular contractions and gallop rhythm, and the blood pressure was 115/80. A few moist rales were heard at the left base and there was 1+ pretibial pitting edema. The patient was digitalized soon after admission. On the fourth hospital day the blood pressure dropped to 92/60 and vasopressor drugs were administered. The subsequent course was uncomplicated and the patient was discharged on the thirty-first hospital day.

As shown in figure 2, the serum GOT obtained 2 hours after onset was normal, but rose by the twenty-first hour to 375 U./ml. Normal values were restored by the fifth post-infarction day.

In table 1 an attempt has been made to relate the GOT results to changes in white blood cell count, erythrocyte sedimentation rate, and body temperature in all patients of group I. It will be noted that the elevation of GOT, in addition to its greater specificity, is generally more striking and hence less equivocal than changes in the other parameters. The peak in serum GOT level was usually reached well before the peak of the white blood cell count or erythrocyte sedimentation rate. It is of interest that carefully recorded body temperatures are shown to be extremely valuable, especially when the differential diagnosis lies between infarction and angina pectoris. The peak of the rectal temperature curve coincides most closely with the peak GOT.

Extension of a known infarct, while often inferred on purely clinical grounds, is frequently difficult or impossible to prove electrocardiographically. There were 5 cases of suspected extension in this group, 3 of which had

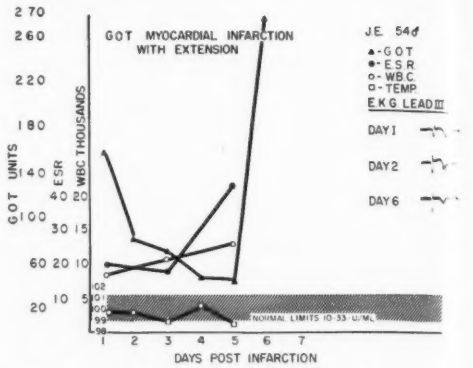

FIG. 3. Results in a case of transmural myocardial infarction showing a dramatic secondary rise in serum GOT correlating with extension occurring on the fifth day after onset.

no further electrocardiographic changes. All 5 showed a clear-cut secondary rise in GOT superimposed upon the usual curve. The following case is typical.

J.E. (fig. 3), a 54-year-old man with known hypertension of 5 years' duration, was admitted on December 3, 1954, because of dull, aching pain along the inner aspects of both arms of 18 hours' duration. The admission electrocardiogram showed a recent posterior infarct, and the initial GOT was markedly elevated. On the third hospital day the blood pressure fell from 160/110 to 92/68 and intravenous pressor drugs were started. A pericardial friction rub was heard from the third to fifth hospital days. On the fifth hospital day the patient became suddenly disoriented and combative, a reaction attributed at the time to opiates. Bibasilar rales were heard for the first time. No unusual changes in the evolving electrocardiographic pattern were noted. However, on the sixth day the serum GOT, which had returned almost to normal levels, rose dramatically to 270 U./ml. The remainder of the hospital course was uneventful.

The degree of elevation of GOT in group I of this series has not been useful in prognosis or as a basis for estimating the size of the infarct. The mean peak in the 12 cases coming to autopsy was 195 U./ml., only slightly higher than the over-all mean peak of 164 U./ml. The highest level observed in 3 cases with infarcts measuring less than 2 cm. in diameter was 191 U./ml., while in 9 cases with infarcts measuring over 2 cm. in diameter, it was 195 U./ml.

Group II. Normal Electrocardiograms

Eighteen cases showed *no* electrocardiographic abnormalities during their course. Six of the 18 were believed on clinical review to be instances of coronary artery disease with angina, in the absence of infarction. In 4 of the 6 cases, the GOT was normal but the remaining 2 had clear-cut elevations and a curve not unlike the group I cases. A summary of 1 of these cases follows.

A.M., a 33-year-old obese man, suffered 3 bouts of squeezing substernal pain just prior to admission, each lasting 10 min. and associated with perspiration, dizziness, and vomiting. Temperature, pulse, and blood pressure were normal and stable throughout the hospital course. The heart and lungs were normal. X-ray pictures of the chest and upper gastrointestinal tract were negative. There was no elevation of white blood cell count or erythrocyte sedimentation rate. The GOT, however, was 50, 80, 30, and 22 U./ml. on the first 4 hospital days. The electrocardiogram remained normal. No convincing diagnosis could be attached to this clinical episode.

Two additional cases in group II showed increased GOT levels. In 1, the final diagnosis was acute cholecystitis with lithiasis. There was no evidence of acute hepatocellular involvement. Although it is possible that the rise in enzyme was due to the gallbladder disease, it should be noted that this was the only elevation observed in 8 cases studied with acute cholecystitis, the majority of which also had cholelithiasis. The second patient, with a discharge diagnosis of postural hypotension, was admitted because of recurrent attacks of syncope without associated symptoms. There was an isolated GOT of 49 U. on the fifth hospital day.

In 14 of the 18 cases with normal electrocardiograms the GOT was also normal. Thus, in 78 per cent of the cases, the clinical appraisal and the GOT results agreed in ruling against infarction.

Group III. ST-T Changes

Eighty-two patients had electrocardiographic changes involving the S-T segment or T wave, or both. The electrocardiograms were interpreted as showing either myocardial ischemia, left ventricular hypertrophy and strain, digitalis effect, subendocardial ischemia, or combinations of these. In no instance was the electrocardiogram sufficiently characteristic to justify the interpretation of myocardial infarction.

In 26 of the 82 cases the clinical and electrocardiographic data supported the diagnosis of infarction; in 21 of these 26 the GOT was elevated. Two representative cases are summarized below.

M.H. (fig. 4), a 64-year-old woman with a history of occasional angina pectoris during the previous year, was admitted because of a severe episode of squeezing anterior chest pain lasting 1 hour. During the week prior to admission there had been more frequent bouts of angina. On admission the blood pressure was 135/85, the pulse 80 and regular. Fine moist rales were present at both lung bases. The electrocardiogram, which was normal a year before the present illness, showed ST-T changes of ischemia in leads I, aV_L, and V_{4-6}.

On admission the serum GOT was 90/ml., returning to normal by the third day. On the fourth hospital day the blood pressure dropped to 106/50. The erythrocyte sedimentation rate was 46 mm./hour on the fifth hospital day. Six months later the electrocardiogram showed a marked reduction in the height of the R-wave in V_4.

H.W., a 56-year-old woman with a history of hypertension, frequent anginal episodes, and left heart failure, was admitted because of 3 days of persistent precordial and left arm pain. The admission blood pressure was 180/110. The erythrocyte sedimentation rate was 23 mm./hour, rising to 34 mm./hour during the first week. On the fourth hospital day pulmonary edema developed, requiring digital-

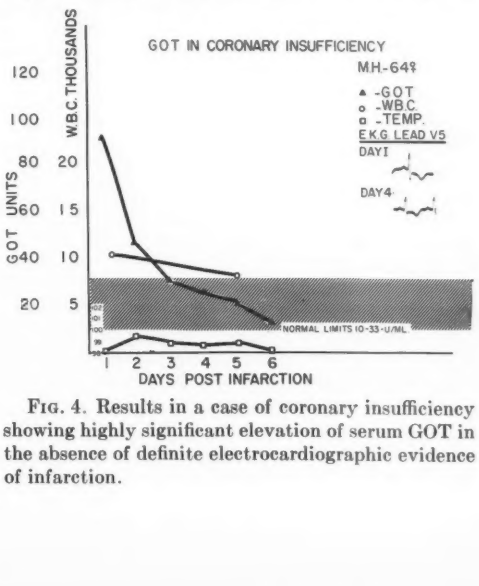

FIG. 4. Results in a case of coronary insufficiency showing highly significant elevation of serum GOT in the absence of definite electrocardiographic evidence of infarction.

ization. By the second week the blood pressure had fallen to 100/70. The temperature remained normal.

The electrocardiogram showed no abnormalities during the first 2 weeks. However, in the third week T-wave inversion appeared and progressed into deeply coved and inverted T waves in the anterior precordial leads. At admission the GOT was strikingly elevated, 250 U./ml., and returned to normal on the third hospital day. In this case, as in the previous 1, the early return of GOT to normal suggests that infarction may have occurred 1 or 2 days prior to admission (fig. 1). It should be noted that the first electric evidence of infarction appeared 19 days after clinical and GOT indications of this infarction.

The entire curve was available for mathematical treatment in 14 of the 21 group III cases with elevated GOT. The average curve showed a peak rise to 102 U./ml. at 30 hours and returned to normal at 64 hours. It is apparent that the patients with only ST and T changes had a lower and more transient elevation in comparison with the group I cases.

The GOT was normal in 5 of the 26 cases that were considered positive for myocardial infarction by the clinical and electrocardiograph appraisal. In 2 of the 5 cases so diagnosed there is no explanation for the discrepancy. However, 3 of the 5 patients came to autopsy and in none was there pathologic evidence of myocardial infarction. The data concerning 1 of these patients are included in some detail.

K.M. (fig. 5), a 59-year-old woman with known hypertension of 5 years' duration, was admitted on December 2, 1954, because of malignant esophageal obstruction requiring surgical relief. The patient was receiving antihypertensive therapy with reserpine at the time of admission. During induction of anesthesia severe shock developed with unobtainable blood pressure. With intravenous pressor medication recovery ensued but surgery was postponed. During this episode the electrocardiogram showed deeply coved and inverted T waves in leads I, II, aV_L, and all precordial leads. These changes persisted for 19 days, showing slight evolution toward normality. At no time was the serum GOT elevated.

On the nineteenth day an esophagectomy and esophagogastrostomy were successfully performed. During surgery all T waves became upright once again. The postoperative course was stormy, the patient developing an esophago-bronchopleuro-cutaneous fistula. On the twenty-first postoperative day inverted T waves appeared in V_1–V_4 and became upright 15 days later. The patient was discharged on the thirty-seventh postoperative day. Five months later she was admitted to the Clinical Center, National Institutes of Health, because of progression of the malignancy and died on July 13, 1955. Autopsy was performed by Dr. Louis Thomas and the following details were taken from his report:

"The heart weighed 340 Gm. There was slight left ventricular hypertrophy and marked dilatation of the right atrium and ventricle. This acute cor pulmonale was caused by thrombotic and tumorous occlusion of many small pulmonary vessels. . . . *The coronary arteries were carefully examined and found to have thin, collapsed walls with empty lumens. No atheromatous plaques were seen.* The myocardium was reddish-brown and firm. No gross areas of fibrosis or hemorrhage were seen.

"Microscopically . . . the small intramuscular branches of the coronary arteries were slightly thickened due to perivascular fibrosis. None of these smaller vessels was occluded by thrombi. . . . No areas of hemorrhage or acute necrosis of cardiac muscle were seen. One microscopic area of fibrosis in the myocardium was seen. This zone of scarring was approximately 2 mm. in greatest diameter and around its periphery were a few hemosiderinophages. No acutely necrotic or degenerated myocardium was seen around this old microscopic focus of myocardial necrosis."

The single minute area of fibrosis was considered inadequate to explain the acute hypotension and extensive electrocardiographic changes recorded. It is more likely that the peripheral collapse was due to the anesthesia and reserpine. Coakley, Alpert, and Boling have observed circulatory collapse during anesthesia in patients receiving reserpine.[12]

The clinical and electrocardiographic appraisal was considered to be negative for

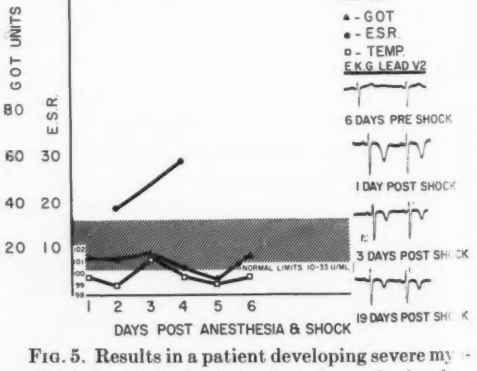

FIG. 5. Results in a patient developing severe myocardial ischemia during induction of anesthesia without elevation of serum GOT (group III).

acute myocardial infarction in 56 of the 82 cases in group III. The GOT was normal and in agreement in 45 of the 56 cases. Of the 11 cases with elevated GOT, 6 were found to have noncardiac causes, such as pulmonary infarction[4] and acute pancreatitis.[2] The clinical appraisal was proved incorrect in 2 of the 11 cases in which autopsy revealed recent myocardial infarction. In the remaining 3 cases the disagreement between the clinical diagnosis and the transaminase level was unresolved.

In summary, there were 16 cases in which the clinical diagnosis and the GOT value were in disagreement. However, in 5 of the 16 cases autopsy proved the "GOT diagnosis" to be correct. Of the remaining 11 cases, 2 had normal GOT values, but were considered clinically positive for infarction. Nine patients had elevated GOT and were considered clinically negative for infarction. Although in 6 of the 9 cases, the source of the elevated GOT was determined to be extracardiac, all 11 cases are included as "errors" in GOT diagnosis, giving an over-all positive correlation of 86.6 per cent. With exclusion of the 6 cases having extracardiac causes for GOT elevation the positive correlation becomes 93.9 per cent.

Our review of the group III cases emphasizes that firm conclusions regarding myocardial necrosis based on ST-T changes alone are rarely possible. The only electrocardiographic pattern that appeared to be reliably related to infarction when interpreted in the light of the transaminase results was the appearance of a persistent depression of 2 mm. or more of the J-junction in the precordial leads.

Group IV. Masking Electrocardiograms

There were 41 patients in the group with "masking" electrocardiograms, that is, electrocardiographic patterns that may conceal or be confused with the pattern of myocardial infarction. In 34 of 41 cases the clinical diagnosis and the "GOT diagnosis" were in agreement, a correlation of 84 per cent.

Fourteen of the 41 cases had bundle-branch block and in 11 of these a diagnosis of myocardial infarction was made on clinical grounds. Ten of the 11 had distinct elevations of the enzyme. A representative example is the patient D.H.

D.H. (fig. 6), a 69-year-old man, was admitted on February 10, 1955 because of dull anterior chest pain of 4 hours' duration associated with dizziness, weakness, vomiting, and cold clammy sweat. On admission the blood pressure was 96/62 and pulse was 84. There were frequent premature ventricular contractions, and a systolic gallop was heard. The initial electrocardiogram was interpreted as right bundle-branch block with S-T changes indicative of an acute myocardial process. A repeat electrocardiogram 7 hours later showed only occasional premature ventricular contractions, the bundle-branch block and S-T changes having disappeared. All subsequent electrocardiograms showed only left bundle-branch block. The GOT curve was characteristic of that seen in acute transmural infarction.

One case with bundle-branch block was diagnosed clinically as myocardial infarction but showed no GOT elevation. In 3 cases with bundle-branch block the clinical review was negative for infarction and none of these patients had elevated GOT levels.

Of 22 cases with residual electrocardiographic changes from previous infarction 9 were determined on clinical grounds to be positive for infarction. Six of the 9 had high serum GOT and 3 were normal. The remaining 13 were not considered to be infarcts on the basis of clinical review. In 10 of the 13, serum GOT was normal and in 3 clearly abnormal. Two of the 3 died during their hospital stay but did not come to autopsy. The third patient had signs and

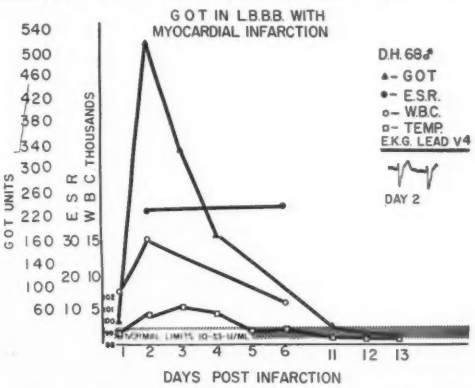

FIG. 6. Results in a patient with left bundle-branch block (group IV) showing a serum GOT curve like that observed in cases of transmural myocardial infarction.

symptoms suggestive of pulmonary infarction, which may have been the cause of the elevated GOT.

Four patients had the clinical findings and S-T and T changes of pericarditis. All had normal GOT levels throughout the serial study. Three other cases of pericarditis in which isolated determinations were made also had normal GOT. Included in this group were patients with uremic pericarditis, idiopathic pericarditis, and metastatic involvement of the pericardium.

A patient with Wolff-Parkinson-White syndrome was included in this group because of a presenting complaint of palpitation and persistent substernal pressing pain. There was no elevation of GOT at any time and the electrocardiogram, which resembled that of posterior myocardial infarction during the first few hospital days, later showed the typical Wolff-Parkinson-White pattern.

Table 2 presents a summary of this study in terms of the correlations in each electrocardiographic group between the transaminase results and the clinical-electrocardiographic

TABLE 2.—*Summary of Clinical-ECG vs. GOT Correlations in Diagnosis of Myocardial Infarction*

ECG Group	No. cases	Clinical evaluation		GOT		% Correlation Clinical vs. GOT
		+	−	+	−	
I: Acute transmural infarction	60	60	0	58	2*	97
II: Normal	18	0	18	4*	14	78
III: LVH and S, myocardial ischemia, digitalis effect, subendocardial ischemia	82	22 2*	48 10*	32	50	86
IV: BBB, WPW, pericarditis, old infarct	41	17 3*	17 4*	21	20	83
Total	201					88

* Indicate the cases in which GOT and Clinical-ECG evaluation were in conflict.

LVH = Left ventricular hypertrophy and strain.

BBB = Bundle-branch block.

WPW = Wolff-Parkinson-White syndrome.

TABLE 3.—*Summary of Autopsy Correlation*

Myocardial necrosis at autopsy	No. cases	Clinical-ECG appraisal			GOT results		
		+	−	% correlation	+	−	% correlation
Present	13	11	2	85	13	0	10
Absent	5*	2	3	60	0	5	10

* In one of these cases both Clinical-ECG appraisal and "GOT diagnosis" were negative but at autopsy 4 months later several old infarcted areas were found that could not be dated.

diagnosis with respect to infarction. A full discussion of each group has already been presented. It will be noted that for the complete series of 201 cases there is a final positive correlation of 88 per cent.

In this group of 201 patients, there were 24 deaths and 18 autopsies. Among the 18 autopsied patients, 2 were considered to be clinically positive for infarction, the electrocardiogram showing serial T-wave inversions. However, GOT levels were normal, and no infarction was demonstrated by gross and microscopic examination of the myocardium. In 2 other cases considered clinically negative for infarction but showing elevated GOT levels, large areas of acute myocardial infarction were found at autopsy. In 3 of the 18 cases electrocardiographic changes of the S-T and T type were present, but the episode studied was listed as negative for myocardial infarction. The serum GOT levels were normal, and at autopsy no acute myocardial infarcts were found. In the remaining 11 cases GOT was elevated, all were considered positive for infarction, and in 10 acute infarcts were found at autopsy. The 1 discrepancy turned out to be nonspecific myocarditis (Fiedler's), with diffuse rather than circumscribed myocardial necrosis.

Table 3 summarizes the autopsy experiences in this study. It serves to emphasize that in every instance the "GOT diagnosis" and the pathologic diagnosis regarding myocardial necrosis were in agreement.

Pulmonary Embolization

Serum GOT was studied in 15 cases diagnosed as pulmonary embolization by clinical

roentgenographic, and electrocardiographic evidence. Eight of the 15 had consistently normal GOT. In 7 of the 15 the values were increased but none rose higher than 85 U./ml. In contrast to the sharp early rise observed in myocardial infarction, the rise in most of these cases did not occur until the fourth to the sixth day after onset of symptoms, often just preceding or concomitant with the appearance of icterus. The cause of the elevation is not clear but may be attributed to the pulmonary necrosis, hemolytic reaction, hepatic dysfunction, or a combination of these.

The elevation of GOT in approximately ½ of the cases of pulmonary embolism coincident with the appearance of jaundice in several suggests that the serum enzyme will be elevated only in those cases that go on to pulmonary infarction. This possibility merits further investigation.

Discussion

In order to evaluate a new diagnostic procedure it is necessary to have an unequivocal means for establishing the true diagnosis. A clinical-pathologic correlation is, of course, the ultimate basis for evaluation. In the 18 cases of this series coming to autopsy, 12 showed recent myocardial infarction and all had an elevated serum GOT in the period immediately following onset. The high levels observed in the autopsied case of Fiedler's myocarditis indicate that *any* form of acute myocardial necrosis may release this enzyme into the serum. That this is indeed the mechanism for the observed elevations of GOT in the serum is shown by the studies of Nydick, Wroblewski, and LaDue.[13] These workers found that normal dog heart muscle contains as much as 465,000 U. of GOT/Gm., whereas infarcted areas contained only 5,000 to 33,000 U./Gm.

Five cases at autopsy showed no evidence of recent myocardial infarction and in none of these was GOT increased. In 1 case there were several old infarcts and it could not be determined if 1 of these had occurred at the time the patient was studied 4 months prior to death, at which time the GOT was negative. Hence, in at least 17 of the 18 cases the "GOT diagnosis" was corroborated by autopsy findings with reference to myocardial necrosis. Also of interest are the 4 autopsied cases in which the clinical-electrocardiographic appraisal was proved incorrect. In all 4 the "GOT diagnosis" was in agreement with the pathologic findings.

With transmural myocardial infarction (group I) the electrocardiographic changes are considered pathognomonic and hence the correlation in this group is probably equivalent to histopathologic proof. We have previously reported high serum GOT in 22 of 24 cases of transmural infarction. A total of 60 such cases has been studied to date and 58 have been confirmed by the enzyme test. These findings firmly establish the association of increased serum GOT with myocardial necrosis. LaDue and Wroblewski have reported 50 cases of transmural infarction, 49 of which had elevated serum GOT.[14] These results in transmural infarction, taken together with the autopsy results in the present series, appear to justify certain conclusions in the interpretation of those cases with equivocal or nondiagnostic electrocardiographic changes. It would seem reasonable to infer that, in the absence of an alternative explanation, the presence of a high serum GOT with a typical curve of evolution supported by either clinical or electrocardiographic evidence of active coronary artery disease justifies the diagnosis of myocardial infarction. If this inference is supported by further studies the very real value of serum GOT in differential diagnosis is clear.

The increase in serum GOT after infarction is transient. In most cases in this series it persisted for 4 to 6 days but in some, especially those with only ST-T wave changes in the electrocardiogram, it was elevated for only 2 or 3 days. This is in agreement with the results of LaDue and Wroblewski,[14] who reported return to normal by the seventh day in all cases and by the third day in 20 per cent of the cases. A single test will most likely be positive if performed 24 to 48 hours after onset of symptoms. However, it is evident that a series of at least 3, and preferably 5, daily determinations is more informative. The rapid rise and almost equally rapid fall in level is characteristic. It will establish in borderline cases that a given value obtained on the first

or second day was indeed above the normal for that individual.

It has been reported[13, 14] that the increase in serum GOT corresponds approximately with the size of the infarcted area. In the few autopsied cases in this series no correlation of this type was noted. However, the rise and fall of GOT during the first few days is so rapid that it is possible to miss the peak concentration in the serum. Further experience is necessary to evaluate the use of serum GOT in estimating the extent of cardiac damage.

Serum GOT promises to be particularly useful in cases like those in group IV, where the electrocardiographic picture is masked or distorted by a previous infarction or by left bundle-branch block. The test should also be of value in the differential diagnosis of pericarditis, since to date all patients with pericarditis, uncomplicated by myocarditis, have had normal values. In addition, Glassner and associates[15] have shown that severe experimental pericarditis in dogs is not associated with elevated serum GOT. Another area in which the test may be helpful is in the diagnosis of extension of a myocardial infarct, which not infrequently fails to declare itself in the electrocardiogram.

It is well recognized that myocardial infarction can occur without the characteristic Q wave in the electrocardiogram. In subendocardial infarction the electrocardiographic picture is fairly well defined. It should be noted that all 4 cases in this series presenting this picture and clinically believed to have had myocardial infarction had abnormal serum GOT. The present findings confirm that certain cases with only S-T and T changes in the electrocardiogram actually have acute myocardial necrosis. Other workers have also noted GOT elevations in patients with S-T and T changes only.[7, 8, 14] As more experience accumulates in the use of this test, it should be possible to improve diagnostic accuracy in establishing the presence or absence of myocardial necrosis. Of course, the ultimate validity of the GOT findings in these cases must await the accumulation of extensive clinical-pathologic correlations.

Agress and associates[16] failed to find an elevated GOT following experimental pulmonary infarction in dogs, but these animals were observed for only 40 hours. We have observed a delayed rise of the enzyme in human subjects. It usually occurs the fourth day after onset of symptoms and rarely exceeds 65 U./ml. The curve is thus quite different from that seen following myocardial infarction. We have detected such elevations only in those cases of pulmonary embolization associated with pulmonary infarction.

TABLE 4.—*Transaminase Value in Other Diseases*

GOT elevated in:	*GOT normal in:*
1. Myocarditis, acute	1. Pericarditis
2. Active hepatocellular damage	2. Angina pectoris or coronary insufficiency
3. Acute pancreatitis	3. Malignant disease
4. Pulmonary infarction	4. Infectious diseases
5. Hemolytic crisis	5. Rheumatic fever without carditis
6. Extensive crushing injuries or burns	6. Acute cholecystitis
7. Surgery	7. Perforated peptic ulcer
	8. Arthritis, rheumatoid and hypertrophic

There are other pathologic conditions besides acute myocardial infarction in which GOT is elevated. These are listed in table 4. The myocarditis may be of rheumatic or nonspecific etiology. The curve of GOT in liver disease generally does not show the rapid rise and fall characteristic of myocardial infarction. Injuries to skeletal muscle must be fairly extensive to cause elevation. A patient with a crush injury and 27 fractures had a serum GOT of 353 U./ml.[17] GOT has been normal in those conditions listed in table 4 when no active hepatocellular disease is concomitantly present.

SUMMARY

The results of serial serum glutamic-oxalacetic transaminase (GOT) assays in 201 cases in which coronary artery disease was suspected are reported. The final positive correlation between the clinical-electrocardiographic diagnosis and the "GOT diagnosis" with respect to acute myocardial infarction was 88 per cent.

In 18 cases coming to autopsy the correlation between elevated serum GOT and recent myocardial necrosis was 100 per cent. Similar elevations were observed in 97 per cent of 70 cases with transmural infarction.

If the clinical and electrocardiographic appraisal for infarction is accepted as the basis of reference, 95 per cent of all cases diagnosed as infarction had elevated serum GOT.

In 18 of 201 cases in which the clinical and electrocardiographic diagnosis was uncertain or negative for infarction there was elevation of serum GOT. Six of these 18 were found to be of noncardiac origin.

It is concluded that the determination of serum GOT provides an additional useful method for the diagnosis of myocardial infarction.

Summario in Interlingua

Es reportate le resultatos de serial essayos de transaminase glutamic-oxalacetic (TGO) del sero in 201 casos con suspicion de morbo de arteria coronari. Le final correlation positive inter le diagnose clinico-electrocardiographic de infarcimento myocardial e le diagnose a TGO de ille condition esseva 88 pro cento.

In 18 casos autopsiate, le correlation inter elevate TGO del sero e recente necrosis myocardial esseva 100 pro cento. Simile elevationes esseva observate in 97 pro cento de 60 casos con infarcimento transmural.

Si on accepta le constatation clinic e electrocardiographic de infarcimento, 95 pro cento del casos diagnosticate como infarcimento monstrava elevate nivellos de TGO seral.

In 18 del casos il habeva elevation de TGO seral in association con diagnoses clinic e electrocardiographic de indecision o negativitate pro infarcimento. In sex de iste 18 casos, le condition del patientes esseva reducite a origines noncardiac.

Nos conclude que le determination de TGO seral provide un utile methodo additional pro le diagnose de infarcimento myocardial.

Acknowledgment

Acknowledgment is made to the following for their assistance and contributions: Drs. Clayton B. Etheridge, Arthur K. Saz, Thomas M. Peery and Israeli A. Jaffe, Mr. Don Baldwin, and Miss Helen Carwood.

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Anomalies of the Coronary Arteries and their Clinical Significance

By RALPH W. ALEXANDER, M.D., AND GEORGE C. GRIFFITH, M.D.

Fifty-four cases with anomalies involving the coronary artery circulation were found among 18,950 autopsies during a 10-year period at the Los Angeles County Hospital. The purpose of this survey is to present the different types of coronary artery anomalies and to elucidate their practical clinical significance.

FIFTY-FOUR cases with anomalies involving the coronary arterial circulation were found among 18,950 autopsies performed during the period from 1940 to 1949, inclusive, at the Los Angeles County Hospital, an incidence of 2.85 per thousand: 38 occurred in males and 16 in females; 3 were Negro and 51 white patients. The distribution of sex and race was similar to that of all autopsies performed at this hospital over the same period. The purpose of this survey is to present the different types of coronary artery anomalies and to elucidate their practical significance in relation to other cardiovascular disease.

The anomalies fall into 2 groups: 39 cases with anomalies of the coronary ostia are presented in table 1; 15 cases with anomalies of the coronary arterial distribution only are presented in table 2. There is no overlapping of cases between the 2 groups.

An attempt has been made to correlate associated cardiac findings, electrocardiographic patterns, and age distribution with these anomalies. Special attention is paid to the incidence of coronary sclerosis, myocardial infarction, and other congenital cardiovascular defects among the patients in these groups.

DISCUSSION

Electrocardiograms had been obtained in 21 out of the 54 cases (tables 1 and 2). In all cases an electrocardiographic diagnosis of myocardial disease was substantiated at autopsy except in 1 (no. 40), where the electrocardiogram was compatible with myocardial infarction but none was found at autopsy. The cause for this electrocardiographic pattern is obscure as it cannot be explained by the relatively minor anomaly of coronary arterial distribution. It is unfortunate that no electrocardiograms were recorded in the 2 children whose coronary circulation originated partly or totally from the pulmonary artery. The patient whose left coronary artery arose from the pulmonary artery (no. 39) had the additional finding of infantile aortic coarctation with a patent ductus arteriosus. The child was symptomless for 3 months after birth and was cyanotic and dyspneic the remaining 2 months of her life. The other patient, whose entire coronary circulation was supplied by the pulmonary artery (no. 38) died 2 days after birth without any coexisting significant cardiac anomaly. The child was delivered at term and was normal in all other respects. The cause of death was listed as atelectasis, although no satisfactory etiology could be found. One might hesitate to attribute the death of the first child to the coronary anomaly in view of the coexisting cardiac defects found. However, death of the second child was in all probability due to the coronary anomaly. It may be concluded that the origin of the entire coronary circulation from the pulmonary artery is incompatible with life, in accord with previous observations.[1, 2]

Nine cases of other congenital cardiovascular anomalies were included in this series—an incidence of 17 per cent. Eight of these occurred in the 39 cases in group 1 (table 1) against only 1 in the 15 cases in group 2 (table 2). Hence, the association of other congenital cardiovascular defects were extremely common in cases of

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TABLE 1.—*Composite Table of Thirty-nine Anomalies of Coronary Ostia (Group 1)*

Type of coronary artery anomaly	Case no., age, sex	Cardiac symptoms and signs	Presumptive electrocardiogram diagnosis	Cause of death	Degree* of coronary sclerosis	Other significant cardiovascular findings at autopsy
Absent right coronary ostium	1 82, F	None	ND	Pulmonary embolism	3	None
	2 40, W	Palpitation	Normal	Thyrotoxicosis	1	None
	3 74, M	Angina pectoris	Posterior infarct	Myocardial infarction	2	Myocardial infarction
	4† 51, M	CHF	Probable myocarditis	SBE (non-hemolytic strep.)	0	Rheumatic mitral and aortic disease with bacterial vegetations
Common ostium in the right sinus of Valsalva	5 9 days, M	Cyanosis 3 days before death	ND	Congenital heart disease	0	Art. arising in rt. vent. supplies upper body; art. from lt. vent. supplies lower body and gives rise to pul. arteries; IVSD; RVH; Patent foramen ovale; Ductus arteriosus
	6 81, M	Hypertension with CHF	Digitalis effect; LVH	HHD; CHF	2	LHV; old posterior myocardial infarct
	7 65, F	Hypertension; Angina pectoris	ND	Myocardial infarct	3	Thrombosis rt. coronary art; recent posterior infarct; LVH
Separate ostia, both in left sinus of Valsalva	8 23, F	None	ND	SBE (Strep. viridans)	0	Bicuspid aortic valve with bacterial vegetations; Hypoplastic aorta
	9 48, F	Hypertension	ND	Cerebral hemorrhage	2	LVH
	10 38, M	Angina pectoris	ND	Myocardial infarction	2	Occlusion rt. coronary art; recent postero-septal-lateral infarct
	11 42, M	None	ND	Bleeding gastric ulcer; perforated duodenal ulcer	0	Fine adhesions base of aortic commissures; wrinkling of aortic arch
	12 1, F	None	ND	Lateral sinus thrombosis	0	None
Separate ostia, both in right sinus of Valsalva	13 67, F	None	Digitalis effect	Pulmonary tuberculosis	0	RVH. LVH.
Both coronary arteries from right sinus of Valsalva but left with 2 ostia	14 53, M	None	ND	Hemophilia with gastric hemorrhage	0	None
Separate ostium of circumflex artery in right sinus of Valsalva	15 53, M	Dyspnea	ND	Bronchial asthma	2	RVH
	16 42, M	Hypertension	ND	Cerebral hemorrhage	2	LVH
	17 66, F	None	ND	Hemorrhagic pancreatitis	1	None
	18 53, M	Hypertension and CHF	RBBB with atrial fibrillation	HHD; CHF; uremia	1	Lt. atrial thrombosis, HHD; old posterior infarct

TABLE 1.—*Continued*

Type of coronary artery anomaly	Case no., age, sex	Cardiac symptoms and signs	Presumptive electrocardiogram diagnosis	Cause of death	Degree* of coronary sclerosis	Other significant cardiovascular findings at autopsy
Three ostia of right coronary artery in normal sinus of Valsalva	19 63, M	None	ND	Ruptured appendiceal abscess	2	Old posteroseptal infarct
	20 22, M	None	ND	Uremia due to congenital anomalies of urinary tract	0	None
Two ostia of right coronary artery in normal sinus of Valsalva	21 60, M	Hypertension	ND	Metastatic prostatic Ca	1	LVH
	22 75, M	Hypertension	ND	Cerebral hemorrhage	3	LVH
	23 63, M	Dyspnea; chest pain	ND	Lobar pneumonia	1	Pericardial effusion; LVH
	24 40, M	None	ND	Metastatic bronchogenic Ca	0	Bicuspid aortic valve
	25 2 mos., M	Cyanosis since birth	ND	Congenital heart disease	0	Aorta from rt. vent. and pul. art. from lt. vent; IVSD; RVH; patent foramen ovale
	26 67, M	CHF	Digitalis effect; possible LVH	HHD; CHF; bronchopneumonia	1	HHD
Ostia of both coronary arteries above sinuses of Valsalva or commissures	27 1, M	None	ND	Tuberculous meningitis	0	None
	28 75, M	Dyspnea, angina pectoris	Possible posteroseptal myocardial infarction	Myocardial infarction	3	Mural thrombosis; LVH; thrombosis of anterior branch of circumflex art; recent anteroseptal infarct
Ostium of left coronary artery above sinus of Valsalva or commissures	29 16, M	Acyanotic congenital heart disease	ND	Streptococcal meningitis	0	Single atrium; IVSD; RVH; aortic hypoplasia
	30 1, M	Acyanotic congenital heart disease	ND	Lateral & longitudinal sinus thrombosis	0	Tetralogy of Fallot; patent ductus arteriosus; patent foramen ovale
	31 59, M	Angina pectoris	Old anterior myocardial infarction	Cerebral thrombosis; myocardial infarction	3	Thrombosis of the rt. coronary art.; old postero-septal and recent posterior infarct; mural thrombosis
Ostium of right coronary artery above sinus of Valsalva or commissures	32 22, F	None	ND	Uremia; chronic glomerulonephritis	0	Uremic pericarditis; LVH
	33 64, F	None	ND	SBE	1	Rheumatic aortic, mitral & tricuspid disease with bacterial vegetations; LVH; RVH
	34 72, M	CHF; angina pectoris	*Entry*—Possible acute posterior myocardial infarction *1 day before death*—Anteroseptal myocardial infarction	Myocardial infarction; CHF	3	Thrombosis of the anterior descending branch of the lt. coronary art.; lt. anterior vent. aneurysm; recent antero-septal infarct

TABLE 1.—*Concluded*

Type of coronary artery anomaly	Case no., age, sex	Cardiac symptoms and signs	Presumptive electrocardiogram diagnosis	Cause of death	Degree* of coronary sclerosis	Other significant cardiovascular findings at autopsy
Ostium of right coronary artery above sinus of Valsalva or commissures—*continued*	35† 26, M	CHF	*2 weeks before death*—Possible acute myocardial infarction *2 days before death*—RVH	CHF due to rheumatic pancarditis	0	Fibrous pericarditis; rheumatic mitral & aortic disease; thrombus in rt. atrium; LVH; RVH
	36 68, M	None	Probably normal	Empyema of of gall-bladder	1	Accessory aortic sinus of Valsalva; the rt. coronary art. originates from the accessory sinus
Hypoplastic left ostium	37 73, M	CHF	ND	CHF due to ASHD	3	Myocardial fibrosis
Both coronary arteries originate from the pulmonary artery	38 2 days, M	Cyanosis since birth	ND	Atelectasis	0	Anatomically patent foramen ovale and ductus arteriosus
Left coronary artery originates from pulmonary artery	39† 5 mos., F	Cyanosis 2 mos. before death; dyspnea; loud murmur	ND	CHF due to congenital heart disease	0	Infantile coarctation of the aorta; Patent ductus arteriosus; LVH; RVH

ASHD—Arteriosclerotic heart disease; Ca—Carcinoma; CHF—Congestive heart failure; HHD—Hypertensive heart disease; IVSD—Interventricular septal defect; LAD—Left axis deviation; LVH—Left ventricular hypertrophy; ND—Not Done; RAD—Right axis deviation; RBBB—Right bundle-branch block; RVH—Right ventricular hypertrophy; SBE—Subacute bacterial endocarditis.

* Degree of coronary sclerosis: 0—none; 1—slight; 2—moderate; 3—marked.

† One of 3 Negroes in group.

anomalies involving the coronary ostia. Anomalies involving coronary arterial distribution, however, did not seem to be associated with a significantly increased incidence of other cardiac anomalies. Seven of the 9 patients with associated other congenital cardiovascular anomalies died within the first 3 decades of life (table 3). The cause of death in 5 of these 7 was the associated congenital cardiovascular disease or a complication thereof. Thus it seems that a high degree of association existed between anomalies of the coronary ostia and other congenital cardiovascular defects.

The degree of coronary sclerosis did not seem to be associated with any specific coronary anomaly but correlated with aging (table 3). No sclerosis was seen in patients who died under 40 years of age. Ten cases of old or recent myocardial infarcts were found in the entire series—an incidence of 19 per cent. As all infarcts occurred in the 41 cases above 40 years of age (the youngest patient with myocardial infarction being 48), the incidence above the fourth decade was 25 per cent. Nine infarcts were demonstrated in the 39 cases in group 1 (table 1) and only 1 in the 15 cases in group 2 (table 2). Again, this observation indicates that anomalies of the coronary ostia are of greater practical significance by far than those of coronary arterial distribution, especially as the age distribution above 40 years was essentially the same in both groups. It must be added, however, that these infarcts did not occur any earlier than could be expected in the general population.

SUMMARY

The incidence of coronary arterial anomalies in a large general hospital was 2.85 per thou-

TABLE 2.—*Composite Table of Fifteen Anomalies of Coronary Arterial Distribution (Group 2)*

Type of coronary artery anomaly	Case no., age, sex	Cardiac symptoms and signs	Presumptive electrocardiogram diagnosis	Cause of death	Degree* of coronary sclerosis	Other significant cardiovascular findings at autopsy
Small right coronary artery. Major supply of area by circumflex artery	40 72, F	CHF	Recent anterior myocardial infarct	CHF; Cor pulmonale	1	RVH; no myocardial infarction identified
	41 80, M	CHF	Premature atrial contractions	Miliary tuberculosis	1	Mild healed rheumatic mitral valvulitis
	42 61, M	CHF	LVH	HHD; CHF; uremia	0	HHD
	43 70, M	CHF	RVH	Pulmonary embolism	2	Healed rheumatic mitral valvulitis
Small circumflex artery. Major supply of area by right coronary artery	44 69, F	CHF	Digitalis effect; LAD	Rheumatic heart disease; CHF; bronchopneumonia	1	Healed rheumatic mitral and aortic valvulitis
	45 83, M	Dyspnea	LAD	Bronchopneumonia	2	Healed rheumatic mitral valvulitis
Circumflex artery a branch of right coronary artery	46 64, F	None	ND	Metastatic sigmoid Ca	2	None
	47 76, M	None	ND	Cerebral hemorrhage	1	LVH
	48 58, M	None	ND	Miliary tuberculosis	1	RVH
	49 82, M	None	LVH	Cerebral thrombosis	2	Healed rheumatic mitral valvulitis
Coronary artery arising in the right sinus of Valsalva has distribution of the left, and artery from the left sinus has distribution of right coronary artery	50 6, F	Dyspnea; cyanosis	RAD	SBE (Strep viridans)	0	Tetralogy of Fallot with bacterial vegetations on pulmonic valve
Accessory branches of the anterior and circumflex branches of the left coronary artery	51 53, M	Hypertension	ND	HHD; CHF	2	LVH
	52 57, M	None	ND	Miliary tuberculosis	0	None
	53 87, F	Hypertension	ND	Cerebral thrombosis	0	LVH
	54 76, M	Hypertension; CHF	Postero-septal infarction	Perforated sigmoid colon; myocardial infarction	3	Mural thrombosis; thrombus in the anterior descending branch of the lt. coronary art.; recent apical septal myocardial infarct

See table 1 for abbreviations.

* Degree of coronary sclerosis: 0—none; 1—slight; 2—moderate; 3—marked.

TABLE 3.—*Age Occurrence of Coronary Anomalies Correlated with Degree of Coronary Sclerosis, Incidence of Myocardial Infarction, and Incidence of Other Congenital Cardiovascular Anomalies*

Decades	No. of cases		No. of cases with degree of coronary sclerosis				No. of cases with old or recent myocardial infarction	No. of cases with other congenital cardiovascular anomalies
	Anomalies at coronary ostia	Anomalies of arterial distribution	None	Slight	Moderate	Marked		
First	7	1*	8*	0	0	0	0	5*
Second	1	0	1	0	0	0	0	1
Third	4	0	4	0	0	0	0	1
Fourth	0	0	0	0	0	0	0	0
Fifth	6	0	2	1	3	0	1	1
Sixth	6	3	2	3	2	1	2	0
Seventh	8	3	2	7	2	1	2	1
Eighth	5	4†	0	2	2	5†	4†	0
Ninth	2	4	0	1	4	1	1	0
Total	39	15	19	14	13	8	10	9

* Includes the only congenital cardiac anomaly found in group 2.
† Includes the only infarct found in group 2.

sand autopsies over a 10-year period. Fifty-four cases are described, 39 with anomalies of the coronary ostia and 15 with anomalies of coronary arterial distribution. No significant correlation could be drawn between the type of anomaly and the degree of coronary sclerosis. One death could probably be attributed to the coronary anomaly itself: this was a case in which both coronary arteries originated from the pulmonary artery and death occurred 2 days after birth. A diagnosis of coronary anomaly was not reflected in the electrocardiograms of the 21 cases in which tracings were obtained.

Ten myocardial infarcts occurred in this series, the earliest at 48 years of age. Nine of the infarcts occurred in the group with anomalies at the coronary ostia. Anomalies of the coronary ostia were commonly associated with other congenital cardiovascular anomalies, accounting for 8 of the 9 cases found in this series. Anomalies of coronary arterial distribution without anomalies at the ostia were of no clinical importance.

ACKNOWLEDGMENT

The assistance of Barbara Benbrook, B.S., is gratefully acknowledged.

SUMMARIO IN INTERLINGUA

Le incidentia de anomalias del arterias coronari in un extense population de hospital general amontava in le curso de 10 annos a 2,85 pro mille autopsias.

Es describite 54 casos, 39 con anomalias del ostios coronari e 15 con anomalias in le distribution del arterias coronari. Nulle correlation significative poteva esser establite inter le typo del anomalias e le grados de sclerosis coronari. Un morte esseva probabilemente attribuibile al anomalia coronari mesme. Isto esseva un caso in que ambe arterias coronari habeva lor origine in le arteria pulmonar, e le morte superveniva 2 dies post le nascentia. In le 21 casos in que electrocardiogrammas esseva obtenite, le diagnose de anomalia coronari non esseva reflectite in le graphicos.

Le serie includeva 10 casos de infarcimento myocardial. Nove de illos occurreva in le gruppo con anomalias del ostios coronari. Anomalias del ostios coronari esseva usualmente associate con altere congenite anomalias cardiovascular. Inter le 9 casos in iste serie in que associate congenite anomalias cardiovascular esseva constatate, 8 habeva anomalias del ostios coronari. Anomalias in le distribution del arterias coronari, in le absentia de anomalias al ostios, esseva sin importantia clinic.

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Hemodynamic and Clinical Appraisal of Coarctation Four to Seven Years after Resection and End-to-End Anastomosis of the Aorta

By J. Leo Wright, M.D., Howard B. Burchell, M.D., Earl H. Wood, M.D., Edgar A. Hines, Jr., M.D., and O. Theron Clagett, M.D.

This study was undertaken to ascertain whether coarctation of the aorta produces permanent hemodynamic abnormalities that may persist despite resection and end-to-end anastomosis. The results of studies in 10 patients 4 to 7 years after operation are compared to those obtained before and immediately after operation. The most significant finding was continued decrease in residual coarctation, in addition to dramatic immediate postoperative improvement in the degree of circulatory impairment.

PREVIOUS studies in this laboratory[1-4] and elsewhere[5] have reported the changes in circulatory dynamics produced by resection of that portion of the aorta affected by coarctation, followed by end-to-end anastomosis. However, these studies were conducted soon after operation and at intervals during the succeeding 18 months. The present report compares the hemodynamic changes in 10 patients studied before and immediately after operation and at intervals during the next 4 to 7 years.

Methods

The long-term study included physical examination, determinations of blood hemoglobin and leukocytes, urinalysis, electrocardiograms, and teleroentgenograms of the thorax. Catheterization of the right side of the heart was performed in addition to puncture of the radial and femoral arteries. Data were recorded by means of the photokymographic methods previously described.[6, 7] Arterial oxygen saturation was monitored during the procedure by means of earpiece oximeters, while oxygen saturation in the chambers of the right heart and the venous inflow tracts was determined by means of the cuvette oximeter.[8] The Van Slyke method[9] of analysis of blood samples was used for determining the cardiac output by means of the Fick principle. A second and independent method, the dye-dilution technic,[10-12] also was used to calculate cardiac output. These determinations were made after the patient was stabilized while breathing 100 per cent oxygen and were done nearly simultaneously to permit comparison of the output by the 2 methods.

The studies were conducted 1 to 2 hours after a light meal and with the patient in the supine position. Premedication consisted of 1½ grains of allyl (1-methylbutyl) barbiturate and ½ grain of codeine.

Results

Clinical Evaluation. All patients were in good health at the time of the long-term study. Two patients (cases 2 and 9, table 1) had had uneventful pregnancies terminated by elective cesarean section (elsewhere) 28 and 42 months, respectively, after surgical correction of the coarctation.

Preoperative systolic murmurs of varying intensity were noted over the precordium in all 10 patients. In 3 instances (cases 1, 7, and 1[illegible]), the murmur was localized to the aortic region. In 2 instances (cases 1 and 4), a relatively prominent and prolonged aortic diastolic murmur suggested associated aortic insufficiency, while a third patient (case 10) had a nonspecific soft diastolic murmur at the base of the heart that disappeared after operation. At the time of the long-term postoperative study, the previously

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heard systolic murmurs were absent in 3 patients (cases 3, 8, and 11), diminished in 3 others (cases 1, 5, and 7) and unchanged in the remaining 4. The aortic diastolic murmurs in cases 1 and 4 were unchanged after operation.

The values for hemoglobin and leukocytes and the results of urinalysis were within the range of normal in all patients.

The preoperative electrocardiograms were compared with electrocardiograms taken 4 to 7 years after operation to determine if any significant change had occurred. Electrocardiographic evidence of decrease in left ventricular hypertrophy was present in only 1 instance (case 2). This change consisted of a decrease in the amplitude and width of the QRS complexes. It is of particular interest that this patient was cured of coarctation as evidenced by the normal pressure ratios obtained after operation (systolic ratio = 1.12; pulse-pressure ratio = 1.21) and the return of pressures above and below the site of coarctation to normotensive values.

Roentgenologic Signs and Cardiac Size. Notching of the ribs was present in 9 of the 10 patients before operation; this was pronounced in 1 patient, moderate in 4, and slight in 4. Teleroentgenograms studied 4 to 7 years after operation showed this notching to be unchanged in 7 patients, while 1 patient had evident diminution of notching of the ribs 6 years after the operation. In the remaining patient, who was 12 years of age at the time of operation, notching of the ribs disappeared nearly completely during the 4 postoperative years.

Changes in cardiac size, measured by the area of the frontal-plane silhouette of the heart,[13] were determined in the 10 patients and expressed as the percentage difference from predicted normal before operation; these values were compared with the percentage difference from predicted normal after operation. In 50 per cent of the patients (cases 2, 4, 5, 9, and 10), the cardiac size ranged from 28 to 60 per cent greater than the size (area) predicted for normal persons of the same height and weight, both preoperatively and postoperatively. While minor postoperative decreases in cardiac size occurred in 5 patients, a pronounced decrease was noted in only 1 patient (case 8).

Hemodynamic Data. Table 1 lists the vital statistics and hemodynamic data in the group of 10 patients (5 males and 5 females) studied an average of 5.3 years after resection of the

TABLE 1.—*Data on Ten Patients Studied Four to Seven Years after Resection of Aortic Coarctation and End-to-end Anastomosis*

Case*	Age, years	Sex	Weight, Kg.	Surface area, $M.^2$	Metabolic rate	Blood pressure, mm. Hg				Cardiac index, L./min./$M.^2$		Peripheral resistance, dynes sec. $cm.^{-5}$	Years after operation
						Radial		Femoral					
						Systolic	Diastolic	Systolic	Diastolic	Fick	Dye		
1	34	M	85	2.04	+64	190	79	150	80	5.5	3.8	1207	5.9
2	36	F	61	1.72	—	142	76	159	79	—	—	—	6.8
3	41	F	65.4	1.75	+18	162	79	156	79	3.9	3.7	1261	4.2
4	39	M	66.3	1.75	+9	151	67	139	71	4.4	4.7	988	4.9
5	37	M	77.7	1.92	+4	171	85	137	81	3.0	3.4	1568	5.6
7	17	F	72.7	1.8	+8	137	64	115	68	3.2	3.6	1221	4.7
8	32	M	79.3	1.98	0	171	97	163	99	2.9	3.3	1693	4.2
9	30	F	45	1.4	—	173	91	163	89	—	3.2	2095	6.1
10	29	M	76.3	1.96	+17	157	74	131	79	4.0	4.2	1045	5.0
11	17	F	50	1.5	—	166	78	140	76	—	3.1	1677	6.1
Normals (26)													
Average.....	28	23 M 3 F	73	1.89	+4	135	71	—	—	3.5	—	1131	—
Range.....	13–44	—	54–93	1.52–2.15	−7 to +20	106–164	58–86	—	—	2.5–5.3	—	745–1569	—

* Case 6 has been omitted.

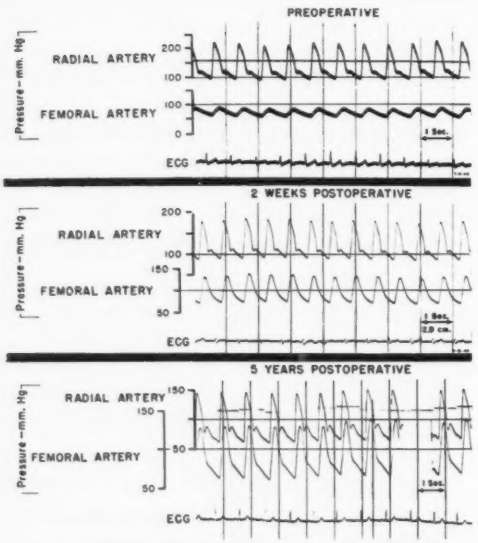

FIG. 1. Intra-arterial radial and femoral pressure pulses in a patient before and after resection of aortic coarctation and end-to-end anastomosis. The significant decrease in both radial systolic and diastolic pressures 2 weeks after operation is followed by a further striking decrease during the next 5 years. The femoral contour shows an immediate change from the saw-toothed appearance in the upper panel with an increase in systolic pressure 2 weeks after operation. The femoral contour becomes more peaked during the ensuing 5 years. The paper speed for the 5-year recording was 25 mm./sec.

coarctation and repair by end-to-end anastomosis of the aorta.

Figure 1 shows a portion of the original records in 1 patient and indicates a significant decrease in radial systolic pressure and a striking increase in femoral systolic pressure 2 weeks after operation, followed by additional improvement 5 years later. The radial diastolic pressure decreased slightly in the early postoperative period, but it was significantly less at the 5-year study. The contours of the radial pulses recorded after operation were not greatly different from those noted preoperatively.

After surgical correction of the coarctation, the femoral systolic pressure showed an initial pronounced increase that was followed in this patient by only a slight additional increase at the 5-year study. The femoral diastolic pressure, which before operation was less than the diastolic pressure above the coarctation (radial artery), continued to be significantly less than simultaneously determined radial diastolic pressure as measured 2 weeks after operation. At the 5-year study, however, the femoral and radial diastolic pressures were essentially equal as a result of the great decrease in the radial diastolic pressure.

The pronounced change in form of the femoral pulse from the characteristic "saw-toothed" preoperative appearance to a contour with greater systolic amplitude 2 weeks after operation was followed by further changes 5 years later, resulting in a contour with a sharper systolic peak and a break on the downward limb that was not seen previously. Although not all the patients showed this pronounced progressive change in the contour of the femoral pulse between the 2-week study and the long-term study, the systolic maximum

TABLE 2.—*Changes in Average Pulse Rates and Simultaneously Measured Radial and Femoral Pressures after Resection of Aortic Coarctation: Ten Patients*

	Pulse rate, beats per min.	Blood pressure, mm. Hg			
		Radial		Femoral	
		Systolic	Diastolic	Systolic	Diastolic
Preoperative values	81 (69 to 100)*	189 (163 to 254)	90 (76 to 105)	108 (92 to 141)	77 (66 to 87)
Change 2 weeks after operation†	+9 (−5 to +36)	−23 (−5 to −42)	−8 (−32 to +5)	+15 (+2 to +59)	−1 (−17 to +1)
Change 4 to 7 years after operation	−6 (−24 to +9)	−30 (−69 to +3)	−10 (−37 to +20)	+34 (+9 to +62)	+1 (−11 to +12)

* Figures in parentheses indicate range.

† Nine patients only.

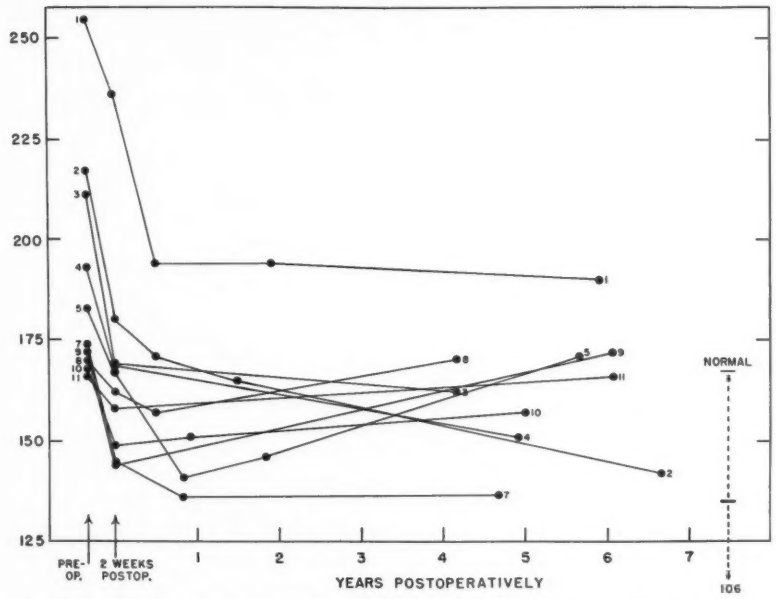

FIG. 2. Changes in intra-arterial radial systolic pressure (ordinate, mm. Hg) in 10 patients with coarctation of the aorta studied preoperatively, 2 weeks after operation and at intervals thereafter to 7 years after operation (39 studies). The average and range of the intra-arterial radial systolic pressure in 26 normal persons in the same age range and studied under similar conditions are included for comparison.

definitely tended to be more peaked in the later records.

Pressures. Table 2 shows the average postoperative change in radial and femoral pressures for the entire group. Early after operation, the average decrease in the radial systolic and diastolic pressures was 23 and 8 mm. Hg, respectively, while the average femoral systolic pressure increased 15 mm. and the femoral diastolic pressure did not show a significant systematic change. The long-term observations indicated further decrease in the average radial systolic and diastolic pressures (table 2) but great variability was present in the group. The femoral systolic pressure had increased an average of 34 mm. Hg at the long-term study.

The radial systolic pressure was plotted against time in years (fig. 2). The normal range and the average radial arterial pressure in 26 normal persons are included for comparison. A sharp decrease in radial systolic pressure 2 weeks after operation was noted in each instance. Five of 6 patients studied during the first year after operation showed further decrease in radial systolic pressure. At the time of the long-term study, the radial systolic pressure had returned to the preoperative level in 2 instances (cases 5 and 9) and had decreased steadily in 3 others (cases 2, 3, and 4), while the remaining cases fell between these 2 extremes.

Figure 3 shows the changes in femoral systolic pressure measured from femoral arterial pressure pulses generated by the same heart beats from which radial systolic pressures were measured. The initial sharp increase in femoral systolic pressure after operation is well shown. Four of 6 patients studied during the first postoperative year showed progressive increases in femoral systolic pressure; in the long-term study, 9 of the 10 patients had femoral arterial systolic pressures greater than those recorded during the initial postoperative study.

The change in radial diastolic pressure (above the site of coarctation) is shown in the

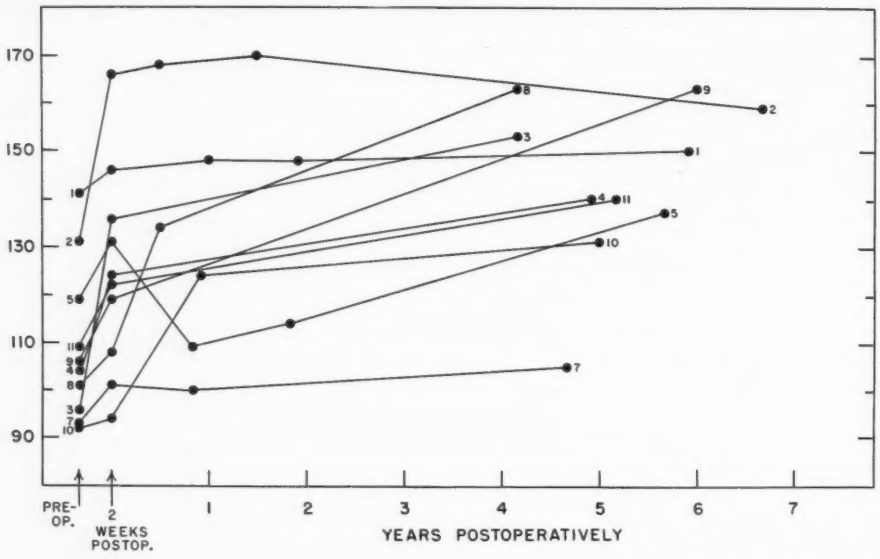

FIG. 3. Postoperative changes in intra-arterial systolic pressure (ordinate, mm. Hg) below the site of coarctation (femoral artery). The pressures were measured from pressure pulses generated by the same heart beat that produced the radial systolic pressures plotted in figure 2. The average and range of femoral systolic pressure in normal persons are not systematically different from the normal values for radial pressure shown in figure 2.

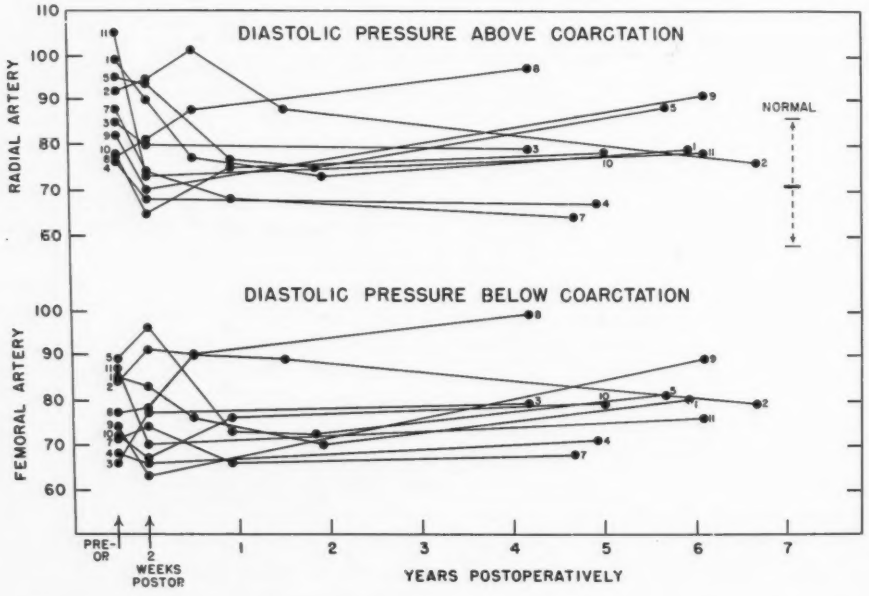

FIG. 4. Comparison of changes in simultaneously recorded diastolic pressure (ordinate, mm. Hg) above and below the site of coarctation (radial and femoral arteries) induced by surgical correction of coarctation of the aorta.

TABLE 3.—*Changes in Ratios between Average Femoral and Radial Pressures and in Time Relationships of Pressure Pulses after Resection of Aortic Coarctation: Ten Patients*

	Ratios, femoral: radial		Delay in onset of femoral pulse, sec.	Femoral pulse build-up time, sec.
	Systolic pressure	Pulse pressure		
Preoperative values	0.57 (0.45 to 0.67)*	0.31 (0.22 to 0.38)	0.03 (0.00 to 0.05)	0.22 (0.18 to 0.25)
Change 2 weeks after operation†	+0.15 (+0.03 to +0.35)	+0.25 (+0.07 to +0.49)	−0.02 (−0.04 to 0.00)	−0.05 (−0.01 to −0.12)
Change 4 to 7 years after operation	+0.33 (+0.15 to +0.52)	+0.49 (+0.27 to +0.83)	−0.03 (−0.05 to 0.00)	−0.05 (−0.02 to −0.13)
Values in normal persons	0.99 (0.94 to 1.05)	1.02 (0.89 to 1.20)	0.00 (−0.01 to +0.01)	0.15 (0.13 to 0.18)

* Figures in parentheses indicate range.
† Nine patients only.

top panel of figure 4, while the change in simultaneously recorded femoral diastolic pressure (below the site of coarctation) is shown in the lower panel. While a striking parallelism generally was noted between the diastolic pressure simultaneously recorded from these 2 sites, points of difference to be noted are (1) the radial diastolic pressure exceeded the femoral diastolic pressure in every case before operation, and (2) 8 of the 10 patients had abrupt and pronounced decreases in radial diastolic pressures 2 weeks after operation, while the femoral diastolic pressure decreased in 5 patients but increased in 5 others.

The significant features in this graph, however, are the progressive changes in the diastolic pressure above and below the site of anastomosis, so that no significant difference existed between them 4 to 7 years after operation. The radial diastolic pressures in 8 of the 10 patients exceeded the average radial diastolic pressure in the normal group at the time of the long-term study.

Time Relationships and Pressure Ratios of Simultaneously Recorded Radial and Femoral Pressure Pulses (*table 3*). The characteristic delay in onset and the prolongation of the build-up time of the femoral pulse were noted in all patients before operation. Similarly, the abnormal (decreased) ratios of femoral to radial pressure were present in all patients. A dramatic change toward normal was noted in all these values 2 weeks after operation. These pressure ratios showed continued significant improvement in the ensuing 4 to 7 years.

This improvement is graphically shown in figure 5, in which the degree of mechanical obstruction produced by the coarctation is expressed by the ratio between femoral and radial systolic pressures in 39 observations in the 10 patients. The average and range found in 9 normal persons are shown on the right of the graph for comparison. Two striking features are evident in this graph; not only did a dramatic decrease take place in the severity of the coarctation 2 weeks after operation but a progressive change was measurable in 1 to 2 years and continued during the long-term study. In spite of this progressive improvement, half the patients failed to reach the range of normal during this time and are considered to have slight to moderate degrees of residual coarctation.

Cardiac Output and Peripheral Arterial Resistance. The cardiac output, radial and femoral pressures, and peripheral arterial resistances measured in these 10 patients are listed in table 1. Cardiac output was determined nearly simultaneously by the Fick and dye-dilution methods in 7 patients. The values for cardiac output in all patients were within the range of normal. Individual variations occurred between the values obtained by the Fick and the dye methods but no systematic difference was noted.

Peripheral arterial resistance (dynes sec. $cm.^{-5}$) was calculated from the Fick data in all except cases 1, 9, and 11, in which the dye-dilution data were used. The peripheral arterial resistance in 3 cases slightly exceeded the upper

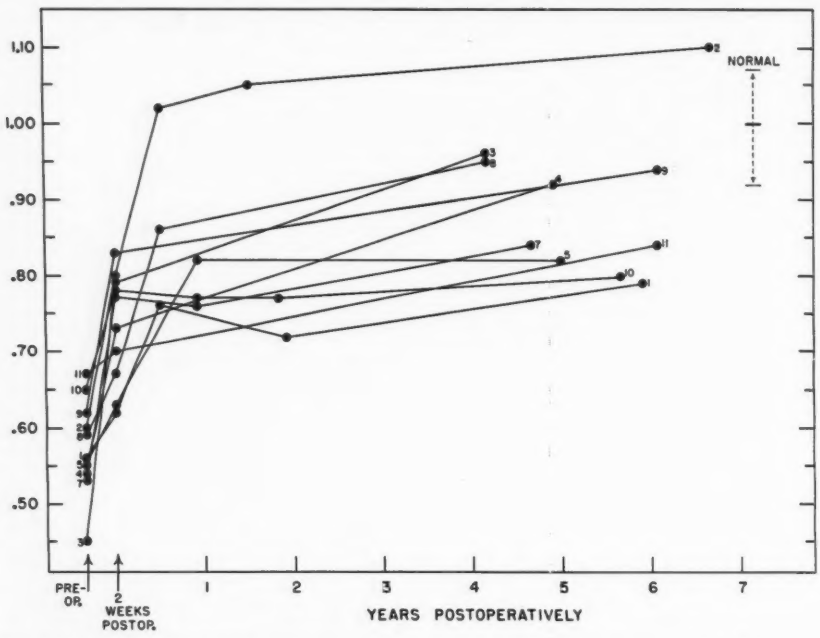

FIG. 5. Change in ratios (ordinate) between femoral and radial systolic pressures after resection of coarctation of the aorta. Note immediate increase in this ratio after operation, followed by a gradual but progressive increase during the next 7 years. Five patients have evidence of a measurable degree of residual coarctation 4 to 7 years after operation.

TABLE 4.—*Average Circulation Times (Seconds) and Time-Component Ratios of Dye-Dilution Curves Following Injection of Dye into Right Ventricle Four to Seven Years after Resection of Aortic Coarctation: Five Patients*

Site of recording	Time components*					Ratios	
	AT	BT	DT	PT	RT	AT/BT	DT/BT
Right ear	8.3 (6.2–9.3)†	6.2 (5.1–7.6)	7.3 (5.4–8.5)	13.5 (11.2–16.1)	18.6 (16.7–20.8)	1.36 (1.05–1.82)	1.17 (0.93–1.43)
Left ear	8.2 (7.3–9.2)	6.6 (5.8–8.6)	6.9 (4.6–9.4)	13.6 (11.0–18.2)	18.4 (16.7–20.8)	1.27 (0.95–1.47)	1.04 (0.72–1.34)
Right radial artery	12.1 (9.6–14.8)	7.1 (5.7–9.9)	8.2 (7.3–9.6)	15.3 (13.0–19.5)	18.0 (15.8–19.5)	1.77 (1.49–2.3)	1.17 (0.97–1.28)

* Symbols are as follows[14]: AT = appearance time; BT = build-up time; DT = disappearance time; PT = passage time; RT = recirculation time.

† Figures in parentheses indicate range.

range of peripheral resistance determined in 26 normal persons studied under similar conditions.

Circulation Times. Qualitatively, the contours of all the dye-dilution curves were within the range of normal. In 5 patients, dye was injected into the right ventricle and recorded at the ears and radial artery (table 4). All the time components and ratios are within the range of normal. The appearance time was significantly shorter at the ears than at the radial artery, but recirculation times were essentially the same at these 2 sites.

DISCUSSION

The most significant finding in our study was the continued decrease in residual coarctation as measured by the ratios of the femoral sy-

tolic and pulse pressures to the same pressures in the radial artery. The data indicate dramatic decrease in obstruction in the early postoperative period, followed by further slow continued decrease in the degree of residual coarctation during the ensuing 4 to 7 years.

As a measure of the impedance to transmission of systolic pressure from regions above the coarctation to the vessels below it, the ratios between the femoral and the radial systolic and pulse pressures describe in a general way the effect of mechanical obstruction produced by the coarctation, together with the impedance imposed by the circuitous collateral vessels required to transport blood to the region below the coarctation.

Figure 6 compares the relationships of the radial systolic pressure (ordinate) and the ratio between the femoral and radial systolic pressures (abscissa) in 111 patients with coarctation studied before operation, in 62 patients studied postoperatively, and in 16 normal persons. The increase in the ratio between the femoral and radial systolic pressures in the 62 patients observed after operation was associated with a significant decrease in the radial systolic pressure. Although this is not a precisely linear relationship, it reflects in a general way the mechanical factor responsible for the increase of blood pressure above the coarctation; as far as can be determined, it is not influenced by humoral or neurogenic factors that also may serve as auxiliary mechanisms producing hypertension in aortic coarctation.

None of the 10 patients had severe hypertension when they were studied 4 to 7 years after operation, although the systolic and diastolic pressure exceeded the range of normal in cases 5, 8, and 9; in case 1, systolic hypertension alone was observed. The presence of mild to moderate hypertension in these cases was not demonstrably due to either increased cardiac output or a significant degree of residual coarctation as measured by the pressure ratios. As already mentioned, the calculated peripheral resistance exceeded the range of normal in 3 patients (cases 8, 9, and 11). In this small series of studies, it is not possible to conclude that increased cardiac output, a generalized increase in peripheral resistance, or the presence of a small degree of residual coarctation was singly responsible for the tendency for some of these patients to have slightly increased pressures above the site of the previously resected coarctation.

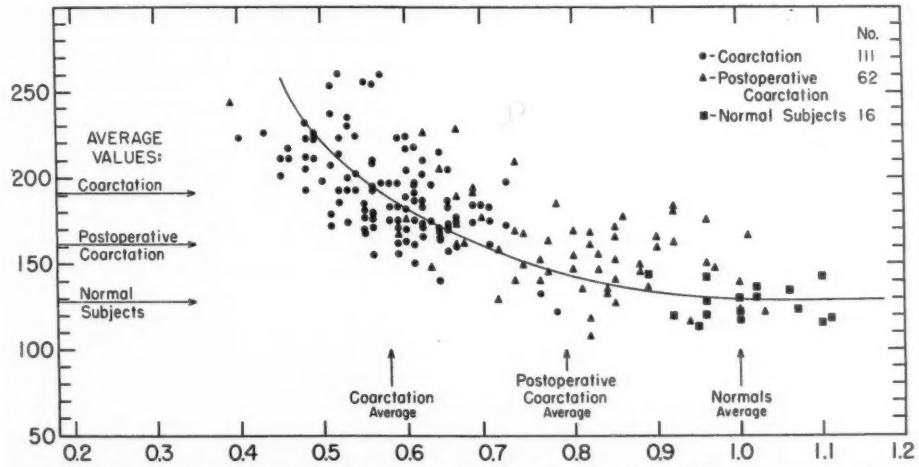

FIG. 6. The relationship of the ratios between the femoral and radial systolic pressures (abscissa) to the radial systolic pressures (ordinate) in 111 patients with coarctation studied preoperatively compared with 62 postoperative studies and the data in 16 normal persons indicates the correlation between the degree of hypertension and the degree of mechanical obstruction, expressed as the ratio of femoral and radial systolic pressures, produced by the coarctation. The significant trend of the pressure ratios toward normal after operation in the 62 patients is associated with a decrease in systolic pressure above the site of coarctation.

Summary

The circulatory dynamics of 10 patients studied before operation and at intervals during the 7 years following resection of aortic coarctation and end-to-end anastomosis are reported.

In addition to dramatic immediate postoperative improvement in the degree of coarctation, measurable continued improvement of a lesser degree occurred in succeeding years. A slight to moderate measurable degree of residual coarctation persisted in 5 patients.

The radial and femoral arterial pressures were within the range of normal in the majority of the patients at the time of the long-term study, and none had a severe degree of hypertension.

The cardiac output of these patients determined 4 to 7 years after operation was within the range of normal, and the calculated peripheral arterial resistance was only slightly increased in 3 patients.

Summario in Interlingua

Es reportate datos relative al hemodynamica de 10 patientes studiate ante le operation e a intervallos durante 7 annos post resection de coarctation aortic e anastomose fin-a-fin del aorta.

A parte le frappante melioration immediatemente post-operatori in le grado de coarctation, continue melioration a grados minus extense occurreva in le curso del annos subsequente. Un mesurabile (leve o moderate) grado de coarctation residue persisteva in 5 patientes.

Le pressiones arterial radial e femoral esseva intra le limites normal in le majoritate del patientes al tempore de iste studio de consecution, e nulle del patientes exhibiva un grado sever de hypertension.

Le rendimento cardiac de iste patientes, determinate a periodos de inter 4 e 7 annos post le operation, esseva intra le limites del norma. Le calculate resistentia arterial peripheral monstrava solmente un leve augmento in 3 patientes.

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A Clinical Correlative Study of the Electrocardiogram in Electrolyte Imbalance

By L. S. Dreifus, M.D. and A. Pick, M.D.

There is no general agreement concerning the action of specific electrolyte disorders and acid-base balance upon the electrocardiogram nor concerning their interrelationships in this respect. In order to test the validity and limitations of the electrocardiographic diagnosis of such disorders in clinical practice, 133 records on 48 patients with suspected or established electrolyte imbalance were compared with chemical determinations, in part serial. Some difficulties encountered in the electrocardiographic diagnosis of mixed electrolyte disorders, and in the distinction of electrolyte from drug effects, are illustrated.

IN ELECTROLYTE imbalance the failure of the electrocardiogram to correlate with clinical and laboratory findings may result in both diagnostic and therapeutic dilemmas. Several authors[1-4] in particular have stressed the lack of conformity of electrocardiographic manifestations with the serum levels of potassium. This disparity has been attributed to the presence of electrocardiographic alterations from other causes or to concomitant abnormalities of other electrolytes. For example, Roberts and Magida[5,6] studied the influence of the acid-base balance experimentally and concluded that electrocardiographic changes suggesting hyperkalemia and hypokalemia could be induced respectively by acidosis and alkalosis, and that such alterations were dependent upon the pH rather than the actual serum potassium concentration. Tarail,[7] on the other hand, was unable to establish any correlation between serum pH, sodium, or calcium with the intensity of potassium effects reflected in clinical electrocardiograms.

Attempts have also been made to clarify the apparent lack of correlation between the electrocardiogram and the actual serum electrolyte concentrations by determining their intracellular/extracellular relationships. Crismon and associates[8] could not relate the intracellular potassium concentration to typical electrocardiographic events in hyperkalemia. Bellet, too, could not establish a definite relationship of the electrocardiographic changes to skeletal muscle potassium content.[9] He considered, among other possibilities, that differences in the metabolic activity of heart and skeletal muscle were the cause of this lack of correlation. His comparison of intracellular to extracellular potassium concentrations with the electrocardiogram gave no better results than serum potassium concentration alone. Kühns,[10] on the other hand, noted such a relationship in animal experiments. In relating intracellular/extracellular potassium concentrations he used a value termed "cardiac potassium quotient" with a normal range of 25 to 32. Reduction of this quotient was associated with typical hyperkalemic changes, and elevation with typical hypokalemic changes in the electrocardiogram. There was, however, no consistency between the electrocardiographic alterations and absolute potassium or sodium concentrations, intracellular or extracellular.

Changes in the autonomic nerve tone and pharmacologic actions of epinephrine, insulin, veratrine, and in particular quinidine, have been noted to simulate electrocardiographic patterns of hypokalemia.[9, 11-13] It is also well known that pre-existent or concomitant alterations of the ST-T segment caused by heart

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Aided in part by the Michael Reese Research Foundation, Hibse Heart Fund, and the Herbert G. Meyer Fund.

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strain, intraventricular block, digitalis medication, coronary disease, hypotension, and hypoxia may prevent, modify, or simulate changes induced by electrolyte imbalance.[9, 14-16]

In view of this multiplicity of factors acting upon the electrocardiogram in conjunction with, or in addition to, the effects of specific electrolyte derangements, an objective study in a diversified hospital population appeared worthwhile in order to gain some idea of the practical value and the limitations of electrocardiographic diagnosis of electrolyte imbalance. In this study special attention was directed to cases in which a correlation could *not* be made and to an analysis of the factors that conceivably may have contributed to the discrepancy between the chemical and electrocardiographic findings. Serial electrocardiograms were compared with serial electrolyte determinations in order to gain information concerning the relative diagnostic value of the two methods in clinical practice.

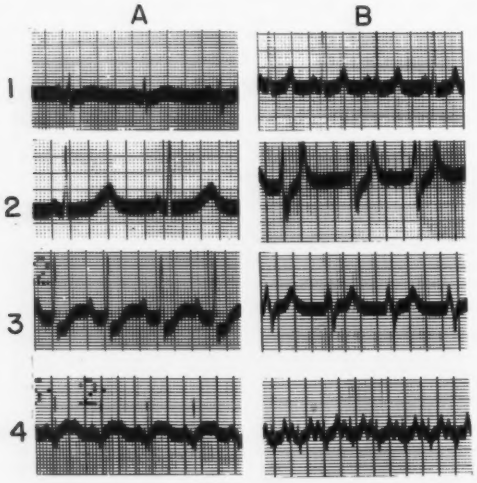

FIG. 1. Examples of gradations of electrocardiographic alterations attributed to potassium depletion *A* and potassium intoxication *B*. Segment B_2 is lead I, all others are lead II. Segments A_4 and B_4 are from infants. A_1. Abdominal carcinoma with massive intestinal hemorrhage. On potassium therapy, K = 4.2 mEq./L., grade +. A_2. Anorexia nervosa, K = 2.7 mEq./L., grade ++. A_3. Severe intractable diarrhea and diabetes insipidus due to carcinoma of the pancreas with metastasis to the hypophysis (demonstrated at autopsy), K = 1.7 mEq./L., grade +++. A_4. Dehydration on potassium therapy, K = 4.0 mEq./L., grade +. B_1. Chronic glomerulonephritis, K (several days before this tracing) = 9.0 mEq./L., grade +. B_2. Polycystic kidneys, uremia, K undetermined, grade ++. B_3. Malignant hypertension, K = 7.38 mEq./L., grade +++. B_4. Dehydration, K = 6.72 mEq./L., grade +.

MATERIAL AND METHODS

One hundred and thirty-three electrocardiograms and corresponding electrolyte determinations obtained in 48 patients were analyzed. The criteria for inclusion in the study were one or more of the following: (1) The electrocardiogram suggested a disturbance in potassium or calcium metabolism, (2) the laboratory data revealed abnormal potassium or calcium blood levels, and (3) electrolyte imbalance was suspected on clinical grounds. The variety of clinical states included is exemplified in the data presented in the legends to figures 1 to 4.

The electrocardiograms were read by one of us without knowledge of the chemical or clinical findings and tabulated according to the suspected electrolyte derangement and the degree of alterations. Afterwards, the serum potassium, sodium, calcium, sodium/potassium ratio and, when possible,

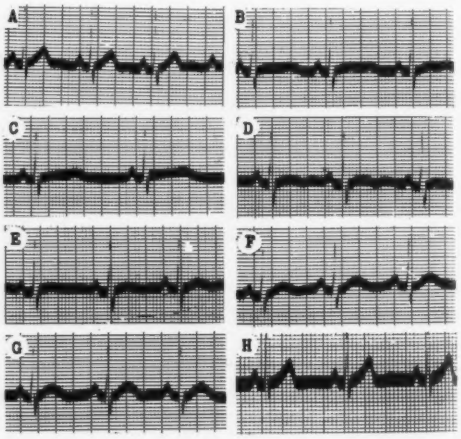

FIG. 2. The sequence of electrocardiographic events (lead II) during an attack of familial periodic paralysis. No potassium determinations were made at this time, but the serum concentration fell to 1.8 mEq./L during another attack. *A*. 7:30 p.m., control; *B*. 2:30 a.m., 2 hours after high carbohydrate meal, paralysis almost complete, only slight movement of right forearm; *C*. 3:15 a.m., complete paralysis of extremities; *D*. 4:35 a.m., 8 minutes after a teaspoon of KCl orally, neck muscles involved, difficulties in coughing; *E*. 4:45 a.m., slight movements of head; *F*. 5:10 a.m., 10 minutes after another teaspoon of KCl, slight movements of fingers and toes; *G*. 5:5 a.m., movements of all extremities; *H*. 9:30 a.m., complete recovery.

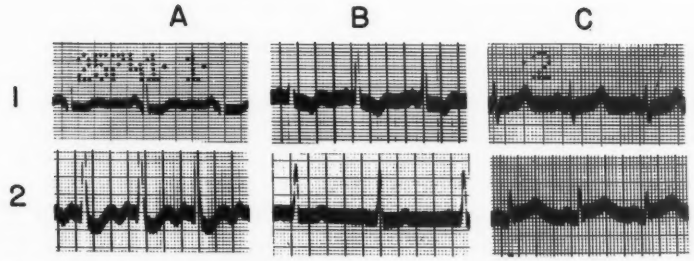

FIG. 3. Examples of electrocardiog aphic alterations interpreted as modifications of a pre-existent left heart strain pattern by hypokalemia *A*, hyperkalemia *B*, and as comb ned effects of pericarditis and hyperkalemia *C*. *A*. Leads I, hypertensive arterioscle otic heart disease. Tracing *2* was obta ned 8 years after *1*, when the patient was in congestive hear fai ure, with a serum potassium of 3.4 mEq./L., *B*. Leads I, malignant hypertension and uremia. Tracing *2* was obtained 2 weeks after *1* when the serum potassium rose to 6.0 mEq./L. *C* Leads II, hypertension with uremia. Tracing *2* was obtained 2 week s after *1* when serum calcium fell to 6.5 mg. per cent and potassium rose to 7.2 mEq./L., with development of a pericardial friction rub.

pH were compared with the electrocardiographic findings. This correlation was also made with respect to changes developing subsequently in serial electrocardiograms and laboratory determinations.

Criteria for the electrocardiographic diagnosis of specific electrolyte disorders were based on numerous exhaustive descriptions in the literature.[9, 14-21] For the determination of the Q-T interval relative to the cycle length, the table of Hegglin and Holzmann[22] was used, and accordingly deviations of more than ±0.04 sec. from the predicted values were considered abnormal. A full account is not given of the varieties of patterns encountered, their sequential development, and preferential manifestation in specific leads. Representative examples of hypokalemic and hyperkalemic alterations, and their gradation as used in this study are illustrated in figure 1, segments 1 to 3. Figure 2 demonstrates acute development of less common features of potassium depletion and their rapid restitution in consecutive records. Diagnostic problems were encountered particularly in infant electrocardiograms, in some cases with pre-existent abnormalities, in simultaneous disorders of the potassium and calcium balance, and in the distinction of hypokalemic alterations from those caused by quinidine medication. Examples of cases in which the electrocardiographic diagnosis was verified, or, on the other hand, proved to be partially or completely incorrect, are shown in figure 1 (segment 4), and figures 3 and 4.

The serum sodium, potassium, and calcium were determined by flame photometry. The serum pH was measured with a Beckman pH meter and microelectrodes and corrected to 38 C. The normal ranges in this study were considered to be: sodium, 137–145 mEq./L.; potassium, 3.8–5.5 mEq./L.; calcium, 9–11 mg. per cent (4.5–5.5 mEq./L.); pH, 7.38–7.47; Na/K ratio, 24–38. Where possible, the serum calcium value was corrected for the serum protein concentration, with a factor of 0.87 for each gram of protein[39] above or below 7.0 Gm. Both corrected and uncorrected calcium determinations were applied in correlations with the alterations of the Q-T duration.

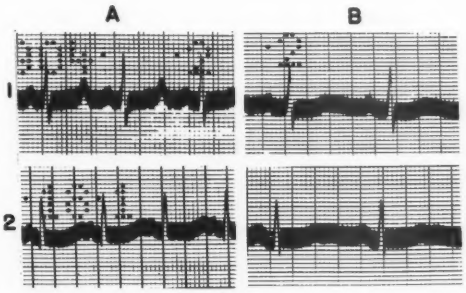

FIG. 4. Examples of difficulties encountered in the electrocardiographic recognition of combined electrolyte disturbances *A*, and in the distinction of hypokalemic from quinidine effects *B*. A_1. Lead II, nephrotic syndrome, Ca = 4.8 mg. per cent, K = 4.2 mEq./L., both hypocalcemia and hyperkalemia were diagnosed in the electrocardiogram. A_2. Lead I, idiopathic nontropical sprue, Ca = 5.3 mg. per cent, K = 3.5 mEq./L., only hypocalcemia was diagnosed in the electrocardiogram. B_1 Lead II, chronic pyloric obstruction, K = 2.7 mEq./L. B_2. Lead II, rheumatic heart disease with recurrent attacks of atrial flutter controlled by quinidine. Note close similarity of B_1 and B_2.

The distribution of the electrocardiographic correlation within the range of serum potassium concentrations encountered in our material and the

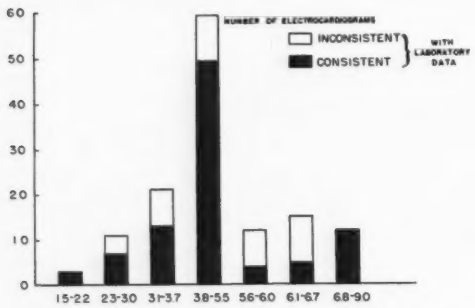

FIG. 5. Diagrammatic representation of the correlation of electrocardiographic findings with the serum potassium concentrations (mEq./L., abscissa) in the ranges encountered in the entire material (cases, ordinate) of this report.

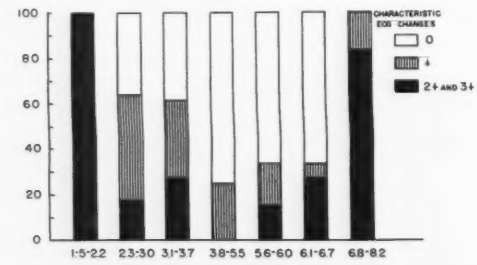

FIG. 6. The distribution of the several degrees of characteristic hypokalemic and hyperkalemic electrocardiographic abnormalities, in relation to the serum potassium concentrations (mEq./L., abscissa) encountered in the entire material of this report (per cent correlation, ordinate).

degree of electrocardiographic abnormalities in these ranges are, respectively, presented in diagrammatic form in figures 5 and 6.

RESULTS

Hypokalemia. There were 35 electrocardiograms (table 1) that suggested hypokalemia, and in 22 of them the serum potassium was actually depressed. In 19 of the 35 instances the Na/K ratio was greater than 38, indicating relative hypokalemia. Thus, the Na/K ratio showed no better correlative value than the actual potassium concentration. The serum pH was in the alkalotic range in 4 of the 13 instances with a normal potassium concentration, but it was within the normal range in an equal number with hypokalemia. Hence, alkalosis per se could not be considered responsible for the electrocardiographic alterations.

TABLE 1.—*Serum Electrolyte Values in Electrocardiograms Suggesting Hypokalemia*

	At time of the electrocardiogram		
No. of Ecgs	K < 3.8 mEq./L.	Na/K > 38	pH > 7.
35	22 (63%)	19	4

TABLE 2.—*Electrocardiographic Manifestation Established Hypokalemia*

No. of instances with K < 3.8 mEq./L.	No. of positive electrocardiograms
35	26 (75%)

On the other hand, in 35 instances in which the serum potassium was lowered, examination of the electrocardiogram (table 2) showed agreement in 26. Here again, the serum Na/K ratio and pH value gave no better correlation than the actual serum potassium concentration.

Follow-up studies were possible in 20 cases with electrocardiographic signs of hypokalemia (table 5), of which 16 (80 per cent) showed a correlation of the electrocardiogram with the serum potassium concentration at one time or another. In 2 instances the electrocardiographic abnormality preceded the fall of serum potassium and in 1 case typical hypokalemic changes persisted after the serum potassium had returned to the normal range. One of the 4 patients, in whom the electrocardiographic diagnosis could not be confirmed, was in congestive heart failure due to rheumatic heart disease with atrial fibrillation and was on digitalis and quinidine medication. In 2 of the other cases a severe disorder of the electrolyte pattern was found, though not of the hypokalemic type. (One of them, with malignant hypertension, had a severe depression of serum sodium to 102 mEq./L.; the other, a diabetic with dehydration, hyperglycemia, and hypernatremia of 165 mEq./L., presented on the whole a hyperosmolarity syndrome.) The fourth patient was hospitalized because of neurasthenia and muscle weakness, and his electrocardiogram became normal after potassium administration; unfortunately, however, electrolyte determinations were not made at this time.

The diagrams in figures 5 and 6 reveal complete agreement between the electrocardiogra

TABLE 3.—*Serum Electrolyte Values in Electrocardiograms Suggesting Hyperkalemia*

	At time of the electrocardiogram		
No. of Ecgs	K > 5.5 mEq./L.	Na/K < 24	pH < 7.38
27	22 (82%)	21	3

and the serum potassium when the concentration of the latter was less than 2.3 mEq./L. Furthermore, in this low range, the severity of electrocardiographic changes shifted *pari passu* with the actual serum potassium concentrations. This was not so true in the group with moderately low serum potassium levels (2.3 to 3.0 mEq./L.) and in the borderline group (3.1 to 3.7 mEq./L.), both as regards to the frequency of noncorrelation and the magnitude of electrocardiographic alterations.

Hyperkalemia. There were 27 instances (table 3) in which the electrocardiogram suggested the presence of hyperkalemia, and the serum potassium was actually elevated in 22 of them. In 21 of these 27 instances the serum Na/K ratio was less than 24, indicating a relative hyperkalemia. Thus, the Na/K ratio was of no greater value in the correlation than the actual serum potassium values. The serum pH was in the acidotic range in 3 of the 5 instances in which the electrocardiogram did not agree with the serum potassium. Since, however, there were other instances with pH in the normal or even alkalotic range in which the potassium determinations were in keeping with the electrocardiographic alterations, the latter could not be ascribed to the acidosis per se.

On the other hand, in 39 instances with elevation of the serum potassium, examination of the electrocardiogram (table 4) showed agreement in 21. Again, the Na/K ratio and the serum pH gave no better correlation than the actual serum potassium concentration.

Follow-up studies were possible in 18 patients with electrocardiographic evidence of hyperkalemia (table 5), and agreement with the serum potassium could be established in 15 (83 per cent). In 2 of these patients the electrocardiogram had anticipated the potassium elevation, while in 2 others the electrocardiographic alterations persisted after the serum potassium concentration had returned to the normal range. Among the 3 patients in whom no such agreement could be established, 2 had chronic glomerulonephritis and were dying in uremia. The third had been receiving potassium medication at the time the electrocardiogram suggested hyperkalemia.

TABLE 4.—*Electrocardiographic Manifestation of Established Hyperkalemia*

No. of instances with K > 5.5 mEq./L.	No. of positive electrocardiograms
39	21 (54%)

TABLE 5.—*Serial Electrocardiograms Compared with Serial Chemical Determinations in Cases with Abnormal Serum Potassium Concentration*

	Hypokalemia	Hyperkalemia
Cases with one or more electrocardiogram(s) suggesting	20	18
Confirmed in serial chemical determinations	16	15
Electrocardiogram(s) anticipated chemical findings	4	2
Chemical anticipated electrocardiogram findings	1	0
Final correlation	80%	83%

The diagrams in figures 5 and 6 reveal complete agreement between the electrocardiogram and the serum potassium concentration in the highest range group (serum potassium above 6.7 mEq./L.) with the severest electrocardiographic changes mostly occurring in this range.

Hypocalcemia (and Hypercalcemia). There were 16 instances in which the electrocardiogram suggested the presence of hypocalcemia (table 6) and in 15 (94 per cent) the serum calcium was actually less than 9 mg. per cent. In 8 of these 16 cases it was possible to correct the calcium values with respect to associated abnormalities of the protein concentration, and in 5, after this refinement, the corrected serum calcium concentration was still less than 9 mg. per cent.

On the other hand, there were 59 instances in which the serum calcium concentration was less than 9 mg. per cent (13 instances in the serum protein-corrected group) (table 7). The electrocardiogram suggested the presence of hypocalcemia in only 15 of these cases (26 per

TABLE 6.—*Laboratory Data in Electrocardiograms Suggesting Hypocalcemia*

	No. of electrocardiograms	Ca < 9.0 mg. %
Total	16	15 (94%)
Corrected for serum protein concentration	8	5 (63%)

TABLE 7.—*Electrocardiographic Manifestation of Established Hypocalcemia*

	No. of instances with Ca < 9.0 mg. %	Positive electrocardiograms
Total	59	15 (26%)
Corrected for serum protein concentration	13	5 (38%)

cent) and in 5 of the 13 instances of the protein-corrected material.

Thus, in contrast to our results with abnormal potassium levels it was not possible to establish a clear-cut serum calcium range below which the electrocardiogram was invariably correlated with the laboratory data.

In this series no case was encountered of *spontaneous* hypercalcemia exceeding 12 mg. per cent, which appears to be the minimal range at which electrocardiographic manifestations can be expected.[9, 23] Hence, this correlation could not be made in the present study.

Hypocalcemia in Association with Potassium Imbalance. Both calcium and potassium were found depressed in 20 instances. We were unable to recognize this combination of electrolyte disturbance in the electrocardiogram. The electrocardiogram in 7 was interpreted as hypokalemic alone, and the presence of hypocalcemia was suspected in 3 other tracings. Serum calcium depression was associated with an elevated potassium in 16 cases. The disturbance of both electrolytes was correctly recognized in 6 in the electrocardiogram. In 7 instances hyperkalemia alone was considered in the electrocardiographic interpretations, and in 2 other instances hypocalcemia alone.

DISCUSSION

On the basis of the present study it would appear that it is easier to diagnose an isolated disorder of the potassium or calcium metabolism in the electrocardiogram than their combination. Figures 5 and 6 reveal, within the ranges of blood potassium levels represented in this series, an excellent correlation in both the lowest and highest ranges (below 2.3 and above 6.7 mEq./L. respectively). Furthermore, the characteristic electrocardiographic alterations were most pronounced in these range groups, which is in agreement with the observations of others.[21, 24] Instances in which such a correlation could not be established were distributed equally within the ranges of 5.6–6.7 and 2.3–3.7 mEq./L. In the normal range (3.8–5.5 mEq./L.), suggestive electrocardiographic alterations were found only in a small percentage. The degree of electrocardiographic abnormalities found in the borderline ranges did not necessarily reflect the extent of the electrolyte disorder as determined in the laboratory. Thus, in the quantitation of the electrolyte derangement, the electrocardiogram cannot be considered a reliable guide, an experience we share with other workers in the field.[25]

Whereas the association of hypocalcemia with hypokalemia proved difficult to recognize, its combination with hyperkalemia was frequently noted in the electrocardiogram. However, even when the diagnosis of the latter combination of electrolyte derangement was missed, at least one or the other of the electrolyte shifts was usually suspected (fig. 4). Surawicz and Lepeschkin[18] and Sjöstrand[13] have dealt with the problem of detecting hypocalcemia in the presence of hypokalemia and vice versa.

An excellent correlation is generally assumed between the electrocardiogram and serum calcium concentrations below 8 mg. per cent.[4, 9, 13] The effects of potassium and calcium are independent of each other and both ions must be administered before the electrocardiogram reverts to normal.[9] In 94 per cent of our cases in which the electrocardiogram suggested hypocalcemia, the serum calcium concentration was less than 9 mg. per cent. But when all instances

with calcium below this range were matched with their electrocardiographic manifestation, a prolonged Q-T interval was found in only 26 per cent. This lack of correlation persisted even in the presence of serum calcium concentrations of 5 mg. per cent or less, and even after correction was allowed for the associated serum protein content. A similar discrepancy between electrocardiographic contour and serum calcium concentrations can also be found in the data presented by others.[21, 23] Determinations of the ionized calcium fraction, which may provide a clue to this problem, were not possible in the present study.

From our data it became clearly evident that, in a correlation of serial electrocardiograms with the broad electrolyte spectrum (including pH and the Na/K ratio), the actual serum potassium concentration correlated best with the electrocardiographic manifestations of electrolyte derangement. Mechanisms by which the electrocardiogram may change under such circumstances have been brought closer to solution by recent studies on cell membrane potentials under the influence of varying electrolyte concentrations of the extracellular perfusion fluid.[26] The mechanisms of similar electrocardiographic alterations induced by epinephrine, veratrine, and quinidine are not well understood. Judging from the electrocardiographic pattern per se, one might suspect that these agents affect the potassium gradient at the cell surface, without any reflection in the serum potassium concentration. In our experience, only the clinical history proved helpful in distinguishing such drug-induced electrocardiographic manifestations from those caused by electrolyte derangement.

Although we tried to correlate serum electrolytes with the electrocardiogram, we are fully aware that the 2 do not measure the same parameters of ionic balance. A determination of merely the serum electrolyte concentrations cannot represent more than a part in the complex system of intracellular-extracellular relationships. Moreover, Joseph, Engle, and Catchpole[27, 28] have recently presented evidence that the ground substance may function as a cation-exchange resin with respect to calcium, sodium, and potassium. Thus, another compartment between intracellular and ordinary extracellular spaces may be operative in the ionic exchange system to induce electrocardiographic alterations in the absence of measurable serum electrolyte changes.

The experimental work of several groups of investigators[5, 6, 29, 30] implies that changes in the serum pH may produce electrocardiographic alterations suggesting potassium derangement in the face of normal serum potassium concentrations. Our data did not permit definite conclusions in this regard. Although it was true that alkalosis was usually associated with hypokalemia, and acidosis with hyperkalemia, no consistency was found in the type and the severity of the electrocardiographic changes with regard to abnormal pH values. At best the latter approximated the correlation accuracy of the serum potassium concentrations with the electrocardiogram.

Some controversy in the literature in relating pH alterations to the intracellular/extracellular potassium (K_i/K_e) ratios seems to have resulted from the fact that acidosis and alkalosis have been produced experimentally under various and not always comparable conditions.[31] In our opinion, changes in the ionic equilibrium resulting from respiratory acidosis or alkalosis may have consequences distinct from those engendered by the production of a metabolic acidosis or alkalosis. Also, insufficient attention has been paid to the differentiation of electrolyte and acid-base disturbances induced in intact and depleted electrolyte states, and in particular in nephrectomized and non-nephrectomized preparations.

From the information at hand[31] it appears that the production of alkalosis causes a shift of the potassium into the cell and a decrease in the K_e/K_i ratio while acidosis acts in the opposite direction, and that these alterations will persist as long as the pH remains abnormal. In nephrectomized animals or in the presence of renal disease with acidosis, small increases in the serum potassium concentration may quickly alter the K_e/K_i ratio and thus produce early and typical changes of hyperkalemia.

Contrariwise, in the presence of alkalosis with intact renal regulatory mechanisms a disturbance of the K_e/K_i ratio may not occur until there is a marked depletion of body potassium, and hence the electrocardiographic alterations can be expected to be delayed. Thus, it is conceivable that the effects of the electrolyte derangement on the electrocardiogram may depend to a significant degree on the presence or absence of renal regulation of the serum electrolytes.

In our material the electrocardiogram anticipated chemical electrolyte disorders in a number of cases, suggesting that the electrocardiogram may reflect changes in the K_e/K_i gradient before actual derangements of the electrolyte balance become evident in their absolute serum concentrations. Our data, in conformity with those of Schwartz and associates[25] do not permit definite conclusion whether an abnormal serum potassium value without concomitant electrocardiographic changes is of greater clinical importance than electrocardiographic findings suggesting an abnormal potassium metabolism in the absence of demonstrable chemical changes. We can only state that once the electrocardiogram per se suggested hyperkalemia or hypokalemia, the latter became evident in the majority of cases in subsequent serial determinations. When serum potassium and the electrocardiogram were in accord, there was of course no doubt about the electrolyte imbalance.

We had relatively little difficulty in diagnosing hypokalemia and hyperkalemia in the face of pre-existing or concomitant electrocardiographic alterations although the typical contour changes were modified to some extent (fig. 3). Sharpey-Schafer[32] showed that T inversion due to heart strain, in contrast to that caused by myocardial infarction, can transiently be abolished by oral administration of potassium chloride, and Langendorf and Pirani[17] were the first to point out that the T-wave configuration in spontaneous hyperkalemia and uremia is the result of a composite effect of several factors acting in opposite direction upon its amplitude and configuration. The combination of S-T elevation caused by uremic pericarditis with hyperkalemic T-wave contour, as illustrated in figure 3, was recognized previously[14, 17, 21] and its reversibility by dialysis demonstrated recently.[3] Whereas the modification of typical strain patterns by hyperkalemia are well known, no definite criteria have been established for the electrocardiographic diagnosis of the not infrequent occurrence of hypokalemic changes in the presence of left heart strain (fig. 3).

It has been shown experimentally that histologic changes consisting in necrosis, cellular infiltration, and fibrosis can be produced in both skeletal and heart muscle by feeding rats potassium-deficient diets.[33, 34] In the heart these lesions are initially localized in the subendocardial layers but may later become diffuse; they may be aggravated by sodium feeding.[35] Necrosis and loss of myofibrils have been attributed to a coagulative action of increased intracellular sodium in the presence of a low potassium[34] or to an intracellular ionic imbalance causing clumping of contractile material and destruction of the adenosine triphosphate-phosphopyruvate system.[36] McAllen[36] has correlated histologic, laboratory, and electrocardiographic alterations produced by hypokalemia in man, while Levine and associates[38] have recently demonstrated that injury currents produced by hyperkalemia in clinical electrocardiograms may result in patterns indistinguishable from those caused by recent myocardial infarction. From all this it would appear that ST-T changes occurring in the presence of hypokalemia and hyperkalemia may have an organic counterpart. Hence, electrolyte imbalance requires immediate correction in order to prevent extensive and perhaps permanent myocardial lesions.

Any study dealing with comparison of electrocardiographic and chemical alterations in the presence of electrolyte imbalance should take into account the known effects of advanced changes of ionic concentrations on cardiac excitability and conductivity.[26, 37] In our material, and within the stated ranges of abnormal serum concentrations of potassium and calcium, disturbances of the cardiac rhythm attributable to the electrolyte im-

balance did not play a significant role and hence their consideration was omitted in the present report.

Summary and Conclusions

An objective comparison in a diversified hospital population with suspected or proved electrolyte imbalance of serum potassium, calcium pH, and sodium/potassium ratios with electrocardiographic findings revealed that, in the presence of abnormal potassium balance, the electrocardiogram correlated best with the actual serum potassium concentrations. Hypocalcemia was almost invariably present when suggested by the electrocardiogram, but in only 24 per cent of all cases with depressed serum calcium was this reflected in the electrocardiogram. Correction for concomitant abnormalities of the serum protein concentration did not lead to a better correlation of the electrocardiogram with the serum calcium concentration.

Full agreement of electrocardiographic and laboratory findings was noted in both the highest (>6.7 mEq./L.) and lowest (<2.3 mEq./L.) serum potassium ranges observed in this study. Failures of the electrocardiogram to reflect abnormal serum potassium levels were equally distributed in the borderline and in the moderately severe range groups. No absolute range could be established for calcium concentrations at which the electrocardiogram can be expected to be diagnostic.

In 15 of 18 cases of hyperkalemia and in 16 of 20 cases of hypokalemia, agreement of electrocardiographic with the chemical laboratory findings could be established after serial studies. In a number of cases the electrocardiogram anticipated the electrolyte derangement. However, no conclusion could be reached as to the relative diagnostic importance of the electrocardiogram and the chemical determinations in a given case.

Possibilities and difficulties in using the electrocardiogram to diagnose specific electrolyte derangements in their most common combinations, or in the presence of preexistent or concomitant electrocardiographic abnormalities of other etiology, are illustrated and discussed.

Possible physiologic bases for the lack of conformity of the electrocardiogram with abnormal serum electrolyte concentrations are considered.

Acknowledgment

We are indebted to Dr. C. Cohn, Director of the Department of Biochemistry, for his aid and his permission to use his data in this study, and to Drs. L. N. Katz and J. Stamler for their critical remarks.

Summario in Interlingua

In un diversificate population hospitalari con suspicite o demonstrate imbalancia electrolytic, un comparation objective del kalium, del pH de calcium, e del proportion de natrium e kalium in le sero con datos electrocardiographic revelava que in le presentia de un anormal balancia de kalium le electrocardiogramma esseva correlationate le melio con le concentrationes de kalium seral. Hypocalcemia esseva trovate de facto in quasi omne casos in que illo esseva suggerite per le electrocardiogramma, sed inter le casos con depression del calcium seral, solmente 24 pro cento reflecteva iste facto in le electrocardiogramma. Correctiones pro simultanee anormalitates del concentration de proteina seral non resultava in un meliorate correlation del electrocardiogramma con le concentration seral de calcium.

Accordos complete del constatationes electrocardiographic e laboratorial esseva notate in le areas maximal e minimal del concentrationes seral de kalium observate in iste studio (i.e. in le areas del valores de plus que 6,7 mEq/L e de minus que 2,3 mEq/L). Le constatation que le electrocardiogramma non reflecteva anormal nivellos seral de kalium esseva equalmente frequente in le areas marginal e in le areas del valores de severitate moderate. Il non esseva possibile establir un area absolute de valores del concentration de calcium ubi on pote expectar que le electrocardiogramma se monstra diagnostic.

In 15 ex 18 casos de hyperkalemia e in 16 ex 20 casos de hypokalemia, accordo del constata-

tiones electrocardiographic con le constatationes chimic de laboratorio esseva establibile post studios serial. In un numero de casos le electrocardiogramma reflecteva le disturbation electrolytic ante que illo esseva chimicamente manifeste. Tamen, nulle conclusion poteva esser derivate in re le importantia diagnostic del electrocardiogramma e del determinationes chimic in le casos individual.

Es illustrate e discutite le possibilitates e le difficultates de usar le electrocardiogramma in le diagnose del disturbationes electrolytic in lor plus commun combinationes o in le presentia de pre-existente o simultanee anormalitates electrocardiographic de altere etiologia.

Es considerate possibile bases physiologic pro le non-conformitate del electrocardiogramma con anormal concentrationes seral del electrolytos.

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Medical Eponyms

By Robert W. Buck, M.D.

Cushing's Disease. Dr. Harvey Cushing (1869–1939) Professor of Surgery, Harvard Medical School, first published his description of "The Basophil Adenomas of the Pituitary Body and their Clinical Manifestations (Pituitary Basophilism)" in the *Bulletin of the Johns Hopkins Hospital* 50: 137–195 (March), 1932.

"A polyglandular syndrome hitherto supposed to be of corticoadrenal origin characterized in its full-blown state by acute plethoric adiposity, by genital dystrophy, by osteoporosis, by vascular hypertension, and so on, has been found at autopsy in six out of eight instances to be associated with a pituitary adenoma which in the three most carefully studied cases has been definitely shown to be composed of basophilic elements, the lesion in one instance having been clinically predicted before its postmortal verification. . . .

"While there is every reason to concede . . . that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal, or with adrenal tumors, the fact, that the peculiar polyglandular syndrome, which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the adrenal cortex other than a possible secondary hyperplasia, will give pathologists reason in the future more carefully to scrutinize the anterior-pituitary for lesions of similar composition."

Bronchial and Arterial Anomalies with Drainage of the Right Lung into the Inferior Vena Cava

By NICHOLAS A. HALASZ, M.D., KATHERINE H. HALLORAN, M.D., AND AVERILL A. LIEBOW, M.D.

Three cases of anomalous pulmonary venous return to the inferior vena cava are presented and 18 previously reported cases are also analyzed. The clinical, radiographic, circulatory and pulmonary function, and anatomic features are carefully detailed. In particular, associated vascular and bronchial anomalies in the lungs were found by preparation of vinylite casts of the pulmonary vessels and bronchial casts; they are of great significance in planning and executing surgical therapy.

INTEREST in major anomalies of pulmonary venous drainage has mounted with the development of methods for accurate clinical diagnosis that have brought the possibilities of corrective surgery into serious consideration. There is a need, therefore, for a careful anatomic study. It is important, also, to determine the incidence and nature of any associated anomalies that might affect therapy.

Anomalous drainage of the pulmonary veins, meaning thereby functional deviation of blood into the systemic venous system, whether by way of a septal defect or otherwise, must be distinguished from anomalous connection, which may imply drainage directly into the right atrium, or some tributary,[1, 2] but may also indicate drainage into the left atrium, by way of an unusual venous channel or postatrial chamber.[3] The basic facts regarding anomalous venous connections of the lungs were collected and excellently analyzed by Brody in 1942.[4] It would appear that total drainage of both lungs into the right atrium or a major tributary occurs half as frequently as partial drainage. In the former, there is always an associated septal defect. With the latter, the drainage is most commonly into the superior vena cava, right atrium, or left innominate vein. In Brody's table, drainage into the inferior vena cava was relatively uncommon, occurring only twice in a total of 65 instances of partial anomalous drainage.

In each of 3 instances of total drainage of the right lung into the inferior vena cava recently observed by the writers, a part of the arterial supply stemmed from the aorta, and there were also associated bronchial anomalies. Not only were there deviations in the pattern of arrangement of the bronchi, but actual abnormalities in structure of a diverticular nature were encountered.

Many of these observations have been reported in isolated instances of this venous anomaly, but that they are commonly associated is suggested by a detailed study. The earlier reports dealt simply with anatomic material.[5-7] Only since 1949 have more recently developed methods been applied that permit an accurate clinical diagnosis of this condition.[8-21] In the present report, data from our 3 patients (see Case Reports and figs. 1–27) will be compared with previously published observations (see table 1). Some published accounts are, unfortunately, rather fragmentary. Certain cases have been cited repeatedly, sometimes with the result that various items of information have had to be pieced together from more than one source.[8, 9, 17, 20]

Clinical Features

General. Among the 21 patients under survey, approximately two-thirds were male. At least 6 of the group had no symptoms whatever.

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Supported by a contract between the Office of Naval Research and Yale University.

TABLE 1.—*Drainage of Right Lung into Inferior Vena Cava, Clinical and Anatomic Data*

Source		Age	Sex	Symptoms		Clinical Observations					Pathology			
				None	SOB	Dex.	EH	PA	Cath.	Angio.	Bronchi	Acc. Art.	Adh.	Heart
C[illegible]assinat[5]	1836	10 da.	♀											+
C[illegible]oper[6]	1836	10 mo.	♀		+	+	+				+	+		
P[illegible]k[7]	1911	2½ mo.	♂			+						+	+	
G[illegible]shman et al[8, 9] A	1949	24 (30)	♂		+		+	+	+	+				
G[illegible]shman et al[8, 9] B		22	♂				+	+						
G[illegible]shman et al[8, 9] C		26	♂				+	+						
D[illegible]tter et al.[10] A	1949	27	♂	+		+				+				
D[illegible]tter et al.[10] B		41	♂	+		+		+	+	+				
F[illegible]edlich et al.[11]	1950	7	♂						+					+
R[illegible]nström and Sigroth[12]	1950		♂				+			+				
W[illegible]lti and Nedey[13]	1950	6	♀	+		+								
D[illegible]ake and Lynch[14]	1950	24	♂			+					+			
Cooke et al.[15]	1951	20	♂	+			+		+	+	+	+	+	
Snellen and Albers[16]	1952	21	♀		+		+		+	+				
Mankin and Burchell[17]	1953	43	♀	+		+	+		+		+			
Bruwer[18]	1953					+	+	+			+			
Sepulveda et al.[19]	1955	55	♂	+			+			+				
Kirklin et al.[32]	1956	32	♀											+
Halasz et al. A	1956	8	♂		±	+	+	+	+	+	+	+	+	+
Halasz et al. B		7	♀			+	+			+	+	+	+	
Halasz et al. C		6 mo.	♀		+	+	+	+		+	+	+		

Note: Only findings recorded as positive are indicated.

Key: SOB—Shortness of breath
Dex.—Dextrocardia
EH—Cardiac enlargement
PA—Enlargement of main trunk of pulmonary artery
Cath.—Catheterization
Angio.—Angiogram
Acc. Art.—Accessory pulmonary artery from aorta
Adh.—Pulmonary adhesions
Heart—Congenital anomaly of heart

Three had severe associated congenital cardiac lesions, in 1 of whom, with transposition of the great vessels, the drainage of the pulmonary veins into the right heart was actually desirable functionally. Only in a few patients were there symptoms and signs that might be ascribed to the venous or associated bronchial anomalies. Five of the patients had shortness of breath, 1 only upon severe exertion. Our 3 patients had repeated respiratory infections and another, reported by Park,[7] died of pneumonia early in life.

The most constant finding upon physical examination was evidence that the heart had been shifted to the right. There was, in some instances, electrocardiographic evidence of right ventricular dominance. There was also, frequently, diminution of resonance in the right hemithorax. In the absence of cardiac anomalies, cyanosis was not present except episodically in the first few days of life in some patients. Pneumonic episodes were attended with appropriate physical signs.

Radiographic Findings. In the plain films the most striking appearance, which should at once suggest the diagnosis, was that of a dagger or scimitar-shaped vascular density more or less parallel to the right cardiac border, but tending to deviate laterally into the lung field near its tapering upper end (figs. 1, 11, 20). The right hemithorax frequently appeared small with narrowed intercostal spaces and a deviation of the heart to the right. The right cardiac border and, in particular, the right atrium, in appropriate oblique views and at fluoroscopy, appeared prominently enlarged, as did the main trunk and left branch of the pulmonary artery (fig. 11). The vascular shadows can be made more prominent by section radiography.

Angiography proved to be useful in demonstrating the opacification of the paracardiac

vascular shadow simultaneously with the pulmonary veins of the contralateral side (figs. 3, 14, 23). The enlargement of the right cardiac chambers was strikingly demonstrated, as were the small right and expanded main and left pulmonary arteries (figs. 3, 13). Evidence of recirculation was the long-maintained opacification of the right cardiac chamber to a time when the pulmonary veins of the left side, and even the aorta, had become opacified (figs. 4, 15, 22, 23). In late films of the angiographic series in 1 of our patients, large arterial vessels were demonstrated to enter the lung from below (fig. 15). The angiographic series have been analyzed to give the temporal sequence of hemodynamic events in each patient (Case Reports).

Bronchography is useful to demonstrate anomalies in distribution and structure of the bronchi. One or more irregular outpouchings were demonstrated in 5 patients, including all 3 of those in the present series (figs. 2, 12, 21). In 2 of our patients the right and left main bronchi were symmetrical, and it was thought that the upper lobe, or both upper and middle lobes, were hypoplastic or absent. However, upon review in the light of the bronchovascular casts prepared in each instance, it was apparent that there was, in fact, a mirror image of the left lung present on the right side (figs. 2, 12). In one other instance, the condition was diagnosed as "hypogenesis."[17] In case 3 of the present series, there was a notably hypoplastic eparterial right upper lobe, compensated in part by accessory bronchi from the medial segment of the large middle lobe (figs. 21 and 25).

Functional Studies. Although cardiac catheterization is not necessary to establish the diagnosis, it is of interest in providing confirmatory evidence of the presence of fully saturated blood within the anomalous vein, or at least of an unusually high oxygen saturation of the blood in the right cardiac chambers.

Some estimate of the magnitude of the recirculation through the right side can be obtained by various methods. If the entire right lung drains into the right side of the heart, and if there are no complicating anomalies on the arterial side, such as accessory pulmonary arteries from the aorta, bronchospirometry will provide information on the relative effective blood flow through the 2 lungs, on the assumption that this is directly proportional to the oxygen uptake of the respective sides. The actual volume of the shunt can be calculated by applying the Fick principle using the oxygen consumption of the normal left lung in the numerator and the difference in oxygen contents between the mixed venous blood in the pulmonary artery and the systemic arterial blood in the denominator. The volume of recirculated blood can then be obtained by subtracting this figure from the right ventricular output, which is obtained by using the total oxygen consumption. Bronchospirometry was performed only in the patient described by Cooke and co-workers.[15] The anomalous right lung in this case accounted for 48.8 per cent of the total oxygen consumption, but it must be noted that there was evidence that only the right lower lobe drained into the right atrium and there was, in addition, at least 1 accessory pulmonary artery from the aorta. In this instance, an attempt was made to estimate the volume of the recirculation to the right lower lobe, but the Fick principle was not correctly applied.

In the absence of bronchospirometric data, a range of values for the relative volume of the recirculation can be obtained by applying a mixing formula, for which the following data are necessary, stated in volumes per cent or per cent oxygen saturation:

1. S = the oxygen content of mixed systemic venous blood (before admixture has occurred in the atrium with the blood brought in by the anomalous vein).

2. T = the oxygen content of blood in the anomalous vein.

3. M = the oxygen saturation of blood in the pulmonary artery (presumably after a thorough mixture of S and T has occurred).

Now let x = the volume of blood arriving from the anomalous vein for every ml. of mixed systemic venous blood. Then, $S + xT = M(x + 1)$. Or $x = \frac{M - S}{T - M}$.

Since S cannot be obtained unless the

relative inflow from the superior and systemic component of the inferior vena cava are known, a very crude approximation can be obtained by assuming the inflow to be equal from these 2 vessels, and averaging the oxygen contents of the superior and inferior vena cavas (from a point distal to the entry of the anomalous vessel). A less spurious way is to calculate the possible range of values by using as S, first, superior vena caval oxygen content and then, separately, the inferior vena caval saturation in the formulas given above. On this basis, the patient reported by Mankin and Burchell[17] (using data supplied in their fig. 2) had recirculation through the right lung amounting to somewhere between 49.8 and 21 per cent of the volume of blood entering the right heart, or of 39 per cent, assuming an equal systemic inflow from the 2 cavas. Mankin and Burchell,[17] however, estimated the magnitude of this shunt as 30 per cent, on the basis of an unstated method.

Further evidence of recirculation through the right lung in the same patient was obtained by Swan, Burchell, and Wood[20] from the study of concentration curves of Evans blue dye in the peripheral vessels, when injected into the right and into the left pulmonary arteries respectively. When applied to the same patient, recirculation was estimated variously as 40 and 35 per cent, values that are within the range calculated in the preceding paragraph.

Whatever its magnitude, the volume of blood recirculated through the right lung in this way is a burden on the right heart, of which the output exceeds that of the left by the magnitude of the shunt.[21] It is of interest that this burden is not usually sufficient in itself to produce cardiac failure, and that most patients with this anomaly can reach adult life.

The blood volume was determined in only 1 patient and was found to be actually less than expected.[15] This result is surprising, inasmuch as patients with a large left-to-right shunt, as through an arteriovenous fistula, usually have an expanded blood volume.[22]

The magnitude of the left-to-right shunt resulting from the accessory pulmonary arterial supply from the aorta has not been measured in these patients, but this must constitute a further increase in the work of the right heart. From observations on experimentally induced collateral circulation to the lung, it appears that even considerable transpulmonary shunts from the aorta through the lung do not significantly affect the thickness and capacity of the left cardiac chambers.[23]

Anatomic Features

Course of the Anomalous Vein. From its termination in the inferior vena cava at the medial and inferior angle of the lobe, the anomalous vein extends upwards and laterally. It may receive its tributaries as small twigs radially arranged at various levels in the manner of a fir tree, and it may not itself branch so as to permit the delimitation of lobes (figs. 6, 8, 16, 17). On the other hand, the vessel may branch near its origin, as in case 3, so that the usual number of lobes can be delimited by penetrating fissures (figs. 26, 27).

Arrangement of the Bronchi. All 3 of the specimens studied display major deviations from the norm in the arrangement of the bronchi. In 2 instances, the pattern is close to that of a mirror image of a left lung (figs. 5, 8, 17). This is suggested even in the bronchogram by the long course and symmetry of the first divisions of the trachea before the upper lobe bronchi are derived. In the casts of cases 1 and 2, it is apparent that the right upper lobe bronchus is hyparterial and that there is a lingular bronchus, but no middle lobe bronchus.

It may be asked whether this arrangement may not represent an upward expansion of lower lobe bronchi, and more specifically those of the superior segments, in consequence of agenesis of the upper and middle lobes. The bronchus interpreted as that of the upper lobe, however, not only possesses branches typical for this lobe, but is, moreover, in both cases 1 and 2, situated anterior to the main trunk of the pulmonary artery, quite the opposite of the relations of a superior segmental bronchus (figs. 7, 17, 18). In case 1, there is an azygos lobe (fig. 9). This is simply a part of the upper lobe separated from the remainder

by the penetrating mesoazygos, but not otherwise disturbed.[24, 25]

In case 3 there is an eparterial upper lobe bronchus, although it lacks anterior branches. These are replaced by upward expansions of rami from the medial branch of the middle lobe bronchus (figs. 25, 27).

Bronchial Diverticula. In each of the specimens there is a bronchial diverticulum. The largest of these is the bifid blindly ending pouch-like diverticulum of case 1 in the position that the medial basal bronchus might occupy were it present (figs. 5, 7). In case 2, there is a small pit corresponding to the position of the anterior segmental bronchus that is not represented as such, but compensated for by some expansion of the branches of neighboring segmental bronchi (fig. 17). This compensation probably took place early in embryonic development, since all regional pulmonary arteries or veins accompany compensating bronchi. In case 3, the aneurysmal widening of the section of the lateral segmental bronchus of the middle lobe might be considered artifact, were it not clearly demonstrated in the bronchogram (figs. 21, 26, 27). From this expanded region there branch bronchi of the usual size and distribution.

Although there is no histologic proof, it is probable that these diverticula represent the seat of chronic suppuration that accounted for much of the symptomatology.

Dextrocardia. The dextroposition of the heart results simply from the mediastinal shift occasioned by the small size of the right lung.

Associated Arterial Anomalies. It is remarkable that, in each of the right lungs of the present series, there were several arteries derived from the aorta as well as a right pulmonary artery of diminished size. The aortic branches were demonstrable in angiograms of 1 patient of the present series (fig. 15), but have previously been noted only at operation or necropsy.

Knowledge of the existence of such vessels is valuable not only in suggesting the presence of left-to-right recirculation, and therefore the relative uselessness in respiration of tissue thus supplied, but also in being forewarned in anticipation of an operative procedure. Since these large arteries often lie within the pulmonary ligaments and in the substance of adhesions, there is a danger that they may be carelessly transected. Such an event may even be fatal.

These arteries substitute for pulmonary arteries of particular segments or subsegments, without overlap. These branches from the aorta, although often beginning their approach to the bronchi from an antihilar direction, yield branches that turn to pursue the direction of and to branch with the smaller bronchial rami, one artery being distributed to each bronchus (fig. 19). They gradually become attenuated with the bronchi to their terminations, in the manner of true pulmonary arteries. These they approximate not only in size, but also in being truly end arteries. There is no evidence that the walls of bronchi are vascularized by them before alveoli appear. In all of these features, they differ from the bronchial arteries, which are generally multiple and plexiform in arrangement and relatively small as compared with the bronchi, the walls of which they richly supply.

Discussion

The very fact that bronchial and vascular anomalies appear to be associated would suggest a common factor in their genesis. No ready explanation, however, presents itself.

The embryologic background for the occasional drainage of the lungs into tributaries of the right atrium is considered to be the presence of a common capillary bed for the ultimate pulmonary veins and branches of the cardinal and umbilicovitelline venous systems, seen most clearly at the early stage when the lungs are represented simply as a diverticulum, soon to become tubular and branching, of the primitive foregut.[26] What is not known are the forces that produce the deviation of drainage, in the present instance unilateral and into the ultimate inferior vena cava. It seems unlikely that small bronchial diverticula could exert any influence upon the drainage of an entire lung or that, on the contrary, the huge anomalous vein could produce these small localized anomalies, while the remainder of the respir-

tor tract remained structurally normal. A ve ige of the original interrelationships of the pu nonary and systemic venous systems is the fr connection of the bronchial and pulmonary ve is in the hilum in the normal lung.

ny aortic blood supply to the lungs is co sidered, on the basis of embryologic studies, to e derived from the primordial postbranchial pl us of the descending thoracic aorta.[27] In th normal course of development this plexus pe sists as bronchial arteries. In the anomalous lu gs of the present series, perhaps the fault lie in the incomplete development of the pu monary artery of the left side by terminal ac retion from components of the postbranchial pu monary plexus. If some of the latter should fai to contribute to the growing extension of the sixth arch, but retain their original connections with the aorta, the ultimate structure would be that actually existing in the specimens under study.

Similar large branches of the aorta have been described to supply "sequestrated" pulmonary tissue and indeed the question of sequestration may well arise in view of the diverticular anomalies that have been described.[28-30] In all 3 instances, however, the anomalous portions of the bronchial tree are not supplied by these aortic branches, but rather apparently normal segments or subsegments. In fact, the present instances supply additional evidence that anomalously developed arteries from the aorta need not result in "sequestration" neither from pressure upon the bronchi nor by any phenomenon of traction, but that they can represent an orderly substitution from the dorsal aorta for vessels normally derived in continuity with the more proximal sixth aortic arch.

Partially,[31] or completely,[32] corrective surgery has been practiced in a few instances of major anomalies of connection of the pulmonary veins. The presence of an associated interatrial septal defect has actually been helpful in some instances in meeting the anatomic problems. Surgical redirection of pulmonary venous blood originally draining into the inferior vena cava from the right lung to the left atrium has been reported only once, in a patient with an associated septal defect.[32] In this instance, the ingenious solution to the problem was to transplant the anomalous vessel to a higher position in the right atrium opposite the defect, and to isolate by suture as a pocket separate from the right atrium opposite the defect, the transplantation site and defect. No other ready solution presents itself in the case of this particular anomaly, since the vein is not sufficiently long to be connected directly to the left atrium. Grafts to increase the length of a vessel for anastomosis are to be considered, but experimental work is needed to determine whether such grafts would take and function without thrombosis under the low pressure gradient prevailing, and in close relation to the actively beating heart.

Study of the present material would suggest certain additional precautions and indications in surgery. It is customary to occlude the pulmonary artery of a lung before preparing the vein for anastomosis. When a lung is supplied by aortic branches, special precautions must be taken, since a very high pulmonary intravascular pressure may otherwise develop. What the fate of the lung might be were these arteries to be permanently occluded is not known. Pneumonectomy should be considered as possibly the best procedure, since the presence of these vessels implies the existence of a left-to-right shunt, since in a considerable proportion of instances, there are also bronchial diverticula, and since the lung is hypoplastic as well.

Case Reports

Case 1

Clinical History. Immediately following birth and on a few occasions during the first year, there were episodes of cyanosis. A physician noted a cardiac bruit at 1 month of age and found, by fluoroscopy, the heart to be shifted to the right. In early childhood there were 2 bouts of pneumonia preceded and followed by chronic upper respiratory infection with cough productive of thick sputum. When exercising heavily during relatively well periods, the patient was noted to have a thin, pale blue line about the lips and to be mildly dyspneic.

The child was first admitted to the Columbia-Presbyterian Medical Center at the age of 4 years, in 1947. He was noted to be retarded physically and to have a congenital coloboma of the left eye and a loud precordial systolic murmur, best heard over the left third interspace. A roentgenogram of

the chest was considered consistent with atelectasis of the right middle lobe and a shift of the heart to the right (fig. 1). At fluoroscopy, there was marked pulsation of the right heart border. An esophagram was read as negative, but a bronchogram showed a right lower lobe bronchiectatic cavity (fig. 2). There was a right axis deviation in the electrocardiogram. Cardiac catheterization demonstrated higher

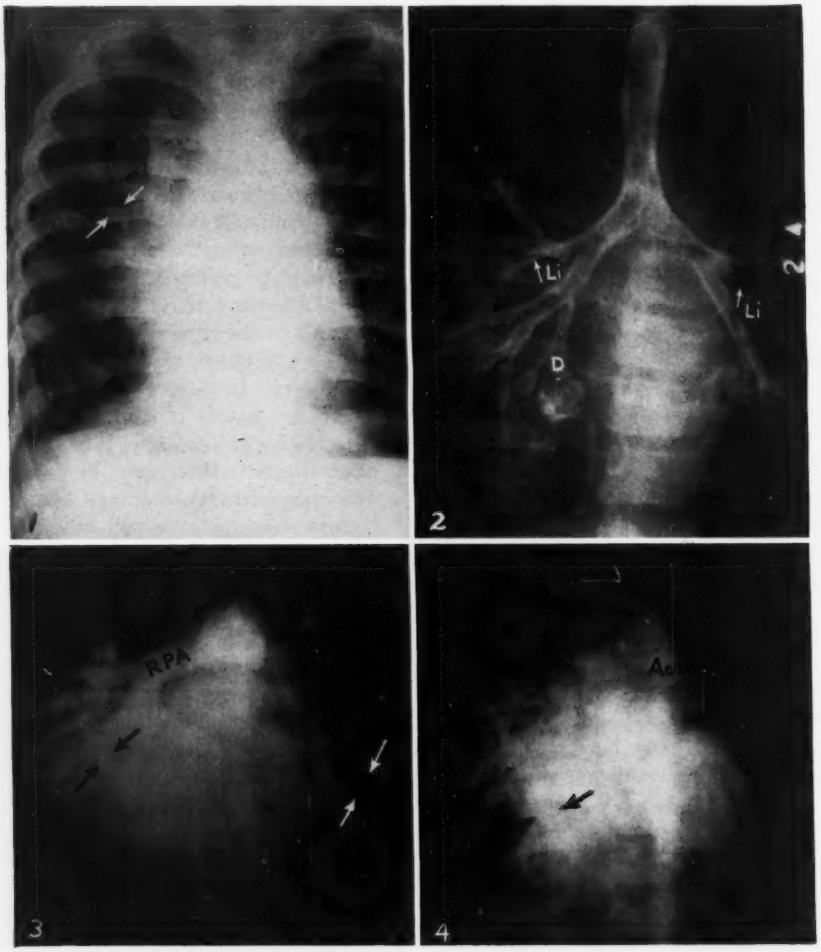


FIG. 1. Case 1. Plain film. The band-like shadow of the anomalous vein is visible (arrows). The fissure demarcating the azygos lobe is seen as a well defined white line extending to the right and upwards from the mediastinum. The heart has a prominent right border and is dextroposed. The right hemithorax is smaller than the left.

FIG. 2. Case 1. Bronchogram. The branching of the trachea is symmetrical and the bronchi of the right side are close to a mirror image of the left. On the right there is a lingula (*Li*) rather than middle lobe (compare with left side). Projecting downwards and medially from the right lower lobe bronchus is a bifid diverticulum (*D*).

FIG. 3. Case 1. Angiogram. The trunk of the pulmonary artery and its right branch (RPA) are both large. An interventricular septal defect may have contributed to this condition. The anomalous pulmonary vein of the right side (arrows) is opacified simultaneously with the left (arrows).

FIG. 4. Case 1. There is persistent opacification of the right cardiac chambers and pulmonary vessels at a time when the contrast medium has already reached the aorta (*Ao*), indicating recirculation of blood through the lungs. The anomalous left pulmonary vein is indicated by arrows.

O_2 values in the right heart than usual, and hypertension in the right heart and pulmonary artery. These observations, taken together with the murmur, were considered to indicate the presence of an interventricular septal defect. The catheter was, unfortunately, not passed into the inferior vena cava. An oblique right apical shadow seen in anteroposterior chest films was interpreted as thickened pleura between upper and lower lobes. At this time the red blood count was 4.7 million, and the hemoglobin was 13 Gm. per cent. Surgery for what was thought to be congenital heart disease and atelectasis was deferred.

Frequent upper respiratory infections and 1 bout of pneumonia occurred between 1947 and 1950. The question of hypoplasia of the right lung was raised. It was decided to admit the patient for resection of the lobe containing the bilobate cystic structure seen on the bronchogram, which was considered to be the source of recurrent suppuration.

Accordingly, he was readmitted in January, 1950. Physical and laboratory findings were as before. At thoracotomy on February 2, 1950, filmy adhesions were encountered in the right hemithorax. An azygos lobe and another single large lobe were found. When the pleural membrane confining the azygos lobe was divided and the lower large single lobe retracted, a large anomalous pulmonary artery was encountered coming into the right hemithorax at the usual level, but looping over the right main bronchus, which, therefore, was hyparterial. No pulmonary veins were present in the usual sites except for a small vein that drained the azygos lobe into the left atrium. However, one vein 1.5 cm. in diameter, another 1 cm. in diameter, and 2 much smaller veins were noted leaving the anteromedial pleural surface of the large lobe near the diaphragm to empty into the inferior vena cava, 4 to 5 cm. below the right atrium. Also in this region were 4 small vessels that were later shown to be arterial; they also ran to the region of the mediastinum in perpendicular fashion. At this point in the exploration the patient became apneic and convulsive and the procedure was terminated without further surgery.

On February 21, 1950, Diodrast was injected and films taken at half-second intervals with a rapid exposure apparatus. The first film showed filling of the superior vena cava and of a portion of the right atrium. A paramediastinal linear shadow in the left side of the thorax was thought to represent an accessory hemiazygos vein or a persistent left superior vena cava. Following filling of the right atrium, the 1½ sec. films showed filling of the right ventricle as well. The shadows of the atrium and ventricle were superimposed and could not be delimited in this single projection. It was clear, however, in these films, that the area occupied by the right atrium and right ventricle was only a small portion of the cardiac shadow, perhaps ⅓ to ⅖. On the 1½-sec. film, a large outflow tract, presumably pulmonary artery, was visible with its most cephalic portion at the level of the third thoracic vertebra, just to the left of the midline. A normal left pulmonary artery was seen with normal distribution of its vessels. There was a large shadow, considered to represent a greatly dilated right pulmonary artery taking origin from the main pulmonary artery (fig. 3). Filling of the left side of the heart was not clearly seen until the 3½-sec. films, and the shadow of the aorta was clearly seen ½ sec. later (fig. 4). The shadow of the aorta appeared normal radiographically. A conspicuous feature of the remainder of the examination was the persistence of filling of the pulmonary vessels. The large anomalous veins seen at the first operation were not discerned as such. The findings were considered to support the roentgen diagnosis of a greatly enlarged right pulmonary artery and interventricular septal defect. The question of arteriovenous fistula was raised and a second exploration was decided upon.

Through the old incision the right lung was again exposed and a thrill noted in the largest of the veins that drained the lung and entered the vena cava. It was thought that either an arteriovenous fistula or simply rapid flow from high to low pressure areas could produce the thrill. The "cystic" zones could not be felt through the lung substance. Because of the anomalous venous drainage of the lung proper, and because of the small size of the azygos lobe, total right pneumonectomy was carried out. It was necessary to tie and cut several small arteries that passed from the aorta directly into the base of the lung.

The cardiac murmur was not altered in the 6 years since operation nor has the heart shadow changed more than to shift slightly farther to the right. Presumably there is still an intracardiac shunt from left-to-right not associated with abnormalities of the left pulmonary vasculature. The patient is retarded in weight and height. He is dyspneic, but not cyanotic. Pulmonary function studies done in February, 1956, demonstrate a bronchospastic element in the dyspnea. There is a family history of asthma, and this is considered as a more important element at present than either the pneumonectomy or the interventricular septal defect.

Anatomic Observations. Thin adhesions covered the specimen. Only a single fissure, that delimiting an azygos lobe, was present. A vinylite plastic bronchovascular cast was prepared. The vessels were injected first, and a radiograph was taken. Then plastic containing 10 per cent lead sulfate was introduced into the bronchial tree and another radiograph was prepared with greater penetration to demonstrate the bronchial tree (figs. 5, 6). After blocks for microscopic section were taken, the tissue was digested away.

After preparation of the cast (figs. 7–10), it was apparent that the lung was anomalous not only in its

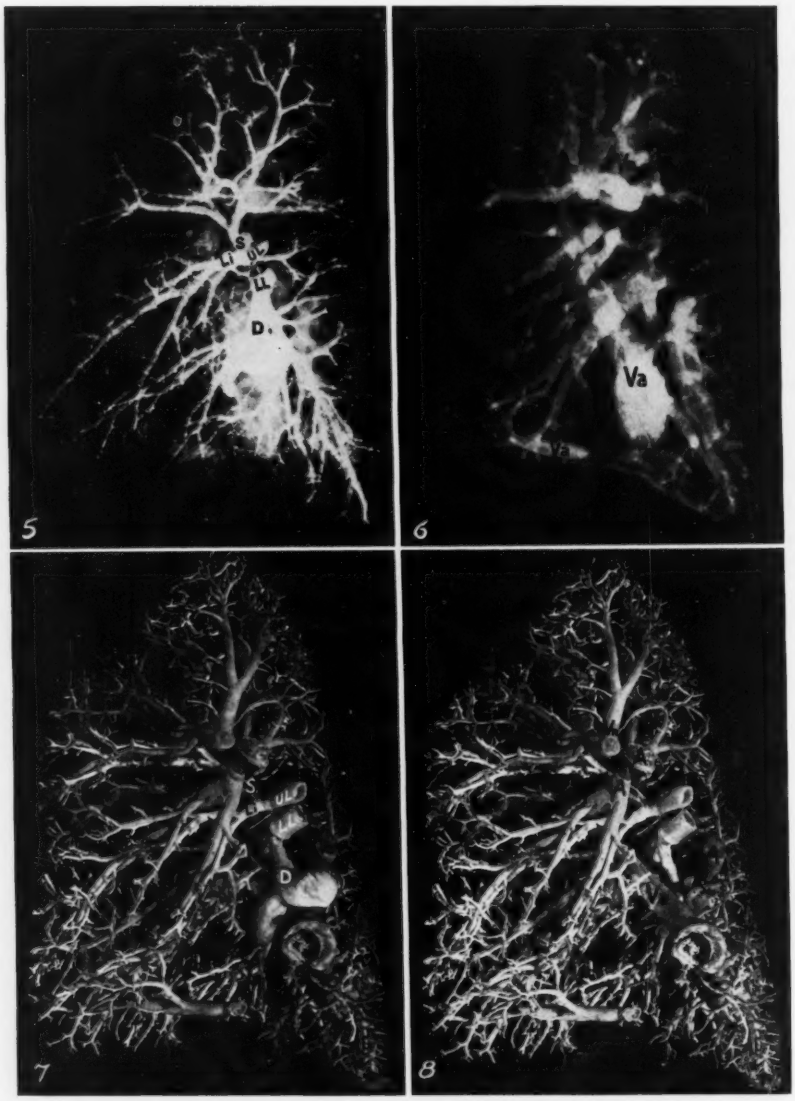


FIG. 5. Case 1. Roentgenogram of cast. The bronchial tree has been filled with plastic containing lead sulfate, and an exposure to yield appropriate contrast has been made. The upper lobe bronchus (*UL*) divides into superior (*S*) and lingular (*Li*) divisions. The diverticulum (*D*) is attached just beyond the origin of the lower lobe bronchus (*LL*).

FIG. 6. Case 1. Roentgenogram of cast made to demonstrate the vessels before the bronchi had been filled. The two anomalous veins (*Va*) are shown. The larger traverses the lobe obliquely. In the azygos lobe is another vein which drains normally into the left atrium (*Vn*). All other vessels shown are arteries.

FIG. 7. Case 1. The cast with diverticulum, labeled for comparison.

FIG. 8. Case 1. The diverticulum removed showing the course of the major veins, labeled for comparison. Arteries (*A*) are derived in a semicircle from a trunk (not present) that looped over the lobar bronchus.

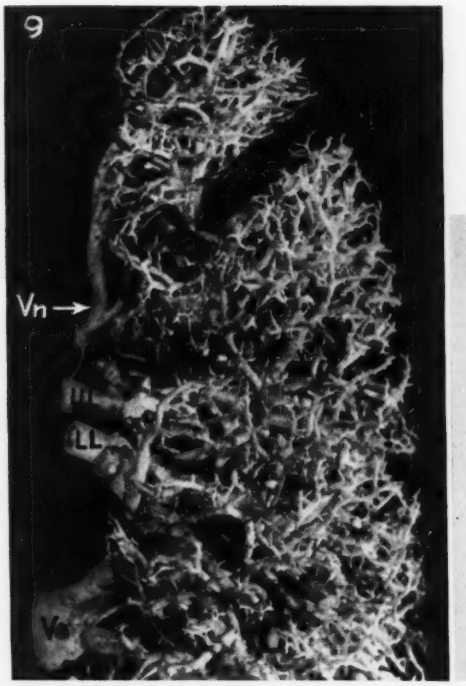


FIG. 9. Case 1. The small azygos lobe is shown clearly demarcated by its fissure in a posterior view of the upper portion of the right lung. *Vn* is the small vein draining the azygos lobe into the left atrium. *Va* is the larger of the anomalous veins.

FIG. 10. Case 1. An accessory pulmonary artery from the aorta (*XPA*) enters the base of the lobe to become associated with a bronchus (*B*) and to terminate in continuity with a tortuous plexus of fine vessels in the pleura (bronchial arteries).

venous drainage, but in other respects—it had the characteristics of a right-sided left lung, in that a lingula rather than a middle lobe was present, and in that the right pulmonary artery looped over the right main bronchus. A small bifid diverticulum was derived from the inferior division of the right main bronchus. This occupied a position corresponding to that of a medial basal segment. The arterial blood supply of this diverticulum was not apparent, but it may have come from bronchial vessels.

The azygos lobe received bronchial components both from the anterior and apical segmental bronchi. This violation of segmental boundaries by the penetrating mesoazygos is commonly observed. It had its own venous drainage by a vessel that was seen at operation to have drained into the left atrium. Most of the remainder of the lung, including parenchyma supplied both by the upper and lower divisions of the right main bronchus was drained by an enormous vein which was said to have entered the inferior vena cava. There was also a smaller additional venous branch running transversely from the base to the lateral aspect of the lobe, which was said likewise to have entered the inferior vena cava.

In the lateral basal segment, a branch from the aorta, injected with black plastic, was found to have substituted for a branch of the pulmonary artery. This vessel, although it had the course and distribution of a pulmonary artery and the typical relationship of a pulmonary artery to the bronchi, terminated in the pleura in a tortuous plexus of fine vessels, that possessed the characteristics of bronchial arteries. The other branches from the aorta were not injected in this specimen.

Case 2

This female child was born on March 16, 1948, after an uneventful gestation. The neonatal period was not remarkable, but toward the end of the third month, she was admitted to a hospital because of episodes of crying and coughing, accompanied by cyanosis of the head and neck. Extensive diagnostic studies were not carried out at this time.

At the age of 6 months, it was found, upon her

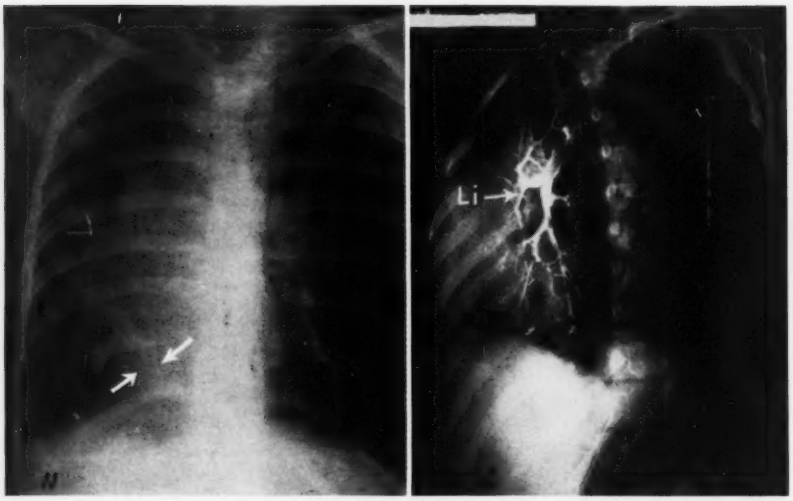


FIG. 11. Case 2. Plain film. Clearly shown against the background of the dextroposed enlarged heart is the tapering anomalous pulmonary vein (arrows). The right hemithorax is smaller than the left.

FIG. 12. Case 2. Bronchogram. The trachea branches symmetrically. Only 2 major bronchi are present in the right lung. Here there is a lingula, but no middle lobe. Extending laterally above the lingular bronchus (*Li*) can be seen a small outpouching of the upper lobe bronchus (compare with fig. 17).

readmission to the hospital, that the trachea and mediastinum were deviated to the right. The breath sounds over the right lung were diminished. The heart was thought to be shifted to the right in consequence of the pulmonary difficulty, and to be devoid of intrinsic pathology. The electrocardiogram gave evidence of dextroposition of the heart. The condition was interpreted as hypoplasia of the right lung, possibly with agenesis of the upper lobe. During the preceding 3 months, she had had recurrent episodes of upper respiratory infections with fever. After this admission, the child seemed improved, but remained underweight and continued to have frequent upper respiratory infections.

In January 1954, she was admitted to the New Haven Hospital for further study of the dextroposition of the heart. At this time, vocal fremitus was increased over the right lower chest, but no rales were heard. The heart was found to be shifted markedly to the right by physical examination and fluoroscopy. Upon review of the chest films, a tapering shadow, apparently venous, was seen extending into the right lung field obliquely upward and outward from the region of the inferior vena cava (fig. 11). The point of maximal cardiac impulse was in the right second intercostal space in the midclavicular line. The blood pressure in the arms was 80/50, and in the legs 100/55. A soft, systolic murmur was heard in the precordial region.

The patient was readmitted on June 27, 1955, for consideration of surgical therapy. At this time, the physical findings were the same as those of the previous admission. Bronchography was performed on July 8, 1955 (fig. 12). The left lung appeared normal. It was thought that the right main bronchus was rather long. Actually, it was shown subsequently by anatomic study to be symmetrical with the left. No upper lobe bronchus was identified, and it was thought that there were "no bronchi in the anterior half of the chest on the right." The pulmonary artery was not discerned. It was thought at this time that there was partial hypoplasia of the right lung, with probable hypoplasia of the right pulmonary artery, and abnormal venous return from the right lung. Angiography was undertaken on July 13, 1955 (figs. 13–15). Moderate enlargement of the right atrium and right ventricle was noted. Branches of the left pulmonary artery in the left lung appeared to be normally distributed. The right pulmonary artery was visualized, but it appeared to be small. The left pulmonary veins emptied into the left atrium, but on the right side all pulmonary veins were collected into a large venous channel that was thought to empty into the vena cava or right atrium. At 1.2 sec., the smaller size of the right pulmonary artery was in sharp contrast with the large trunk and left branch. The pulmonary veins of both sides first became opacified at 2.8 sec. and were sharply outlined at 3.5 sec. The course of the anomalous right pulmonary vein was demonstrated with great

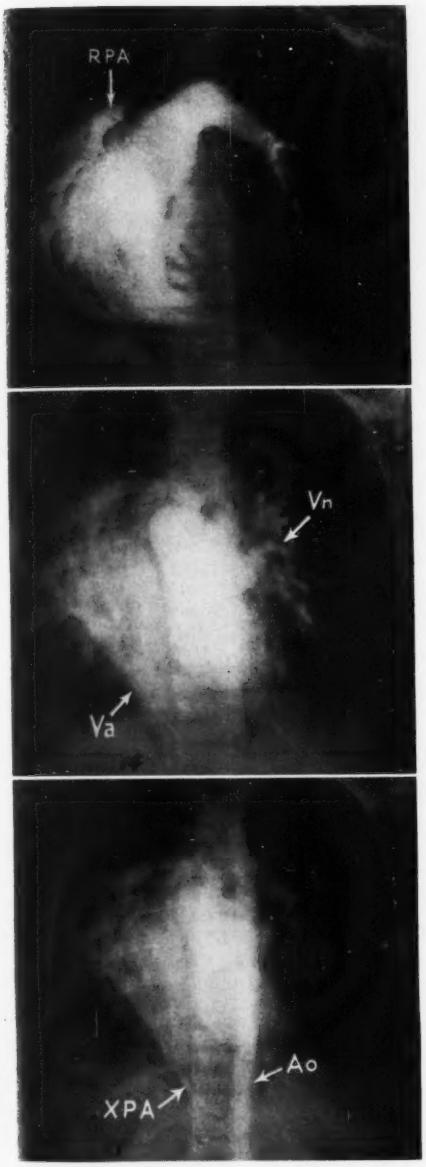


FIG. 13. Case 2. Angiogram. 2.0 sec. The small size of the right pulmonary artery (*RPA*) and the enlarged pulmonary arterial trunk and left pulmonary artery are shown. The cavity of the right ventricle is also enlarged. Prominent interstices among the trabeculae carneae are visible as finger-shaped projections extending medially from the opacified right ventricular chamber.

FIG. 14. Case 2. Angiogram at 4.2 sec. The anomalous pulmonary vein of the right side (*Va*) and the pulmonary veins of the left (*Vn*) are simultaneously opacified.

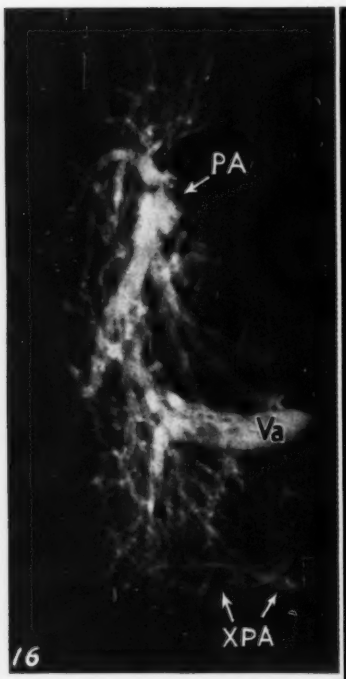
FIG. 15. Case 2. Angiogram at 7.1 sec. Ascending from the aorta (*Ao*) is seen one of the accessory pulmonary arteries (*XPA*). The opacification of the vessels on the right side is maintained in part by recirculation through the pulmonary vessels and in part by the left to right shunt resulting in transfer of contrast medium from the aorta to the right lung through the accessory pulmonary arterial branches.

clarity (fig. 14). At 4.2 sec., the aortic arch first became radiopaque. A large artery was seen to ascend from the aorta to the base of the lung at 6.3 sec. (fig. 15). Even at 13.2 sec. there was still some opacification of the right cardiac chambers, evidence of the long persistence of recirculation. A right thoracotomy was performed on July 19, 1955, in the hope that a surgical anastomosis of the anomalous venous channel to the left atrium might be possible. This, however, proved not to be the case. Five large arteries were found to proceed from the aorta into the substance of the right lung at various levels. A bronchial artery also was found along the right main bronchus. The pleural cavity on the right side was obliterated by adhesions. A pneumonectomy was performed.

Anatomic Observations. The gross specimen was lightly covered with the remnants of adhesions. There was no external fissure. A bronchovascular cast was prepared. The anomalous vessels were well seen in a roentgenogram of the cast (fig. 16). The specimen, although derived from the right hemithorax, was seen in the cast (fig. 17) to possess essentially the structure of a left lung, but with venous drainage entirely into the inferior vena cava, and with 6 arteries derived from the aorta substituting for certain pulmonary arteries.

The right stem bronchus was hyparterial (figs. 17, 18). There were 2 main bronchi, an upper and a lower lobe bronchus. The superior division of the upper lobe bronchus divided into 3 branches of which the anterior was a blindly ending wedge-shaped rudiment. Others comprised the apical and posterior branches. Rami of the latter extended into anterior segmental territory. The inferior division had the structure of a lingula and extended almost to the base of the lobe on the medial aspect. It was here fused within the same pleural membrane as the lower lobe. The lingular bronchus had a small superior and a large inferior branch that sprang from the main lingular stem. The length of the latter was 1.3 cm.

The lower lobe bronchus, after a course of less than 1 cm., yielded a superior segmental bronchus and a common basal bronchus. The latter divided almost symmetrically into an anteromedial basal and common trunk for the lateral and posterior basal segments. These 4 segmental bronchi were of almost equal size.



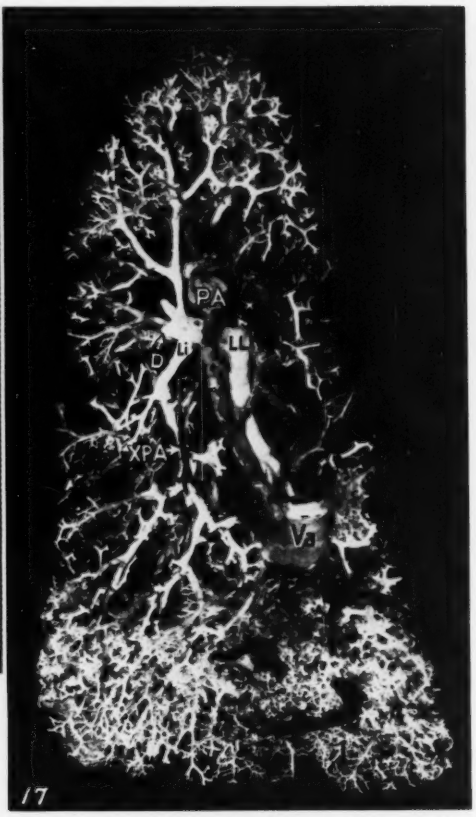


FIG. 16. Case 2. Anteroposterior roentgenogram of cast before digestion of the tissue. *Va* is the anomalous pulmonary vein. The source of its tributaries in all parts of the lung is apparent. The pulmonary artery (*PA*) is also visible. Two large accessory pulmonary vessels (*XPA*) are shown entering the base of the lung from the medial aspect.

FIG. 17. Case 2. The bronchial diverticulum (*D*) is shown extending forward from the upper lobe bronchus, just above the lingular (*Li*). The hyparterial position of the major lobar bronchus is evident. A large accessory pulmonary artery (*XPA*) injected in black is seen along the medial aspect of the inferior lingular bronchus and 3 others are seen entering the base of the lung. *LL* is the lower lobe bronchus.

The arterial supply consisted of a main pulmonary arterial trunk and of 6 "accessory pulmonary arteries" derived from the aorta. The pulmonary artery looped over the left main bronchus and supplied all of the lung in a fashion typical for that of the left pulmonary artery, but in mirror image, except for those portions that were supplied by accessory pulmonary arteries. These comprised portions of the lingular and medial, anterior, and lateral basal segments, and all of the posterior basal. All of the accessory pulmonary arteries, except the lingular, swept laterally from the posteroinferior angle of the lower lobe. The largest of these vessels was one that supplied the lateral basal segment. The relations of these vessels to the bronchi were of interest; although the major arterial trunks approached the bronchi from the periphery of the lung, the actual bronchial branches became applied to the bronchi in a fashion characteristic of pulmonary arteries. None of these arteries had the spiral anastomosing characteristics of a bronchial artery, despite their aortic origin (fig. 19). There was no overlap in the territory supplied by the pulmonary and accessory pulmonary arteries.

The anomalous vein had 2 major tributaries, both of which ran obliquely upwards and forwards from a point near the posterior and inferior corner of the lobe. The smaller branch passed laterally into the fork of the left main bronchus where it drained the apical and a part of the posterior segments and the

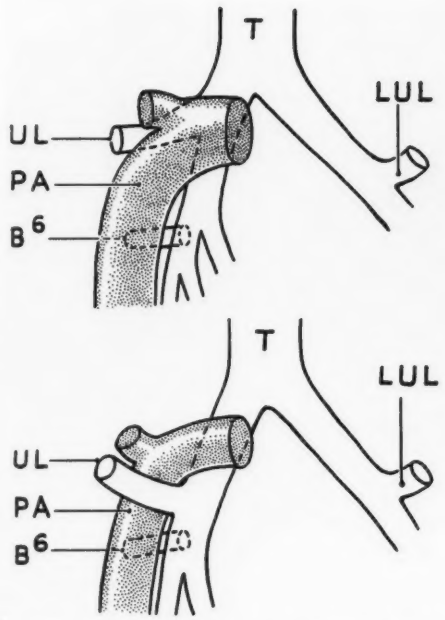


FIG. 18. The relation of the main trunk of the pulmonary artery to the bronchi in a "right sided left lung" (as seen in cases 1 and 2 of present series) is shown in the lower half of the figure. The normal status is indicated for comparison in the upper half. In the former, the branching of the trachea is symmetrical, the stem bronchus is long, and the upper lobe bronchus is hyparterial. It is evident that the superior segmental bronchus of the lower lobe (B^6), in contrast with the upper lobe bronchus, is posterior to the trunk of the pulmonary artery in both the normal and anomalous lungs.

lingula. The larger branch swang upwards and laterally to the bifurcation of the left lower lobe bronchus and drained the remainder of the lung, i.e., the entire lower lobe and those parts of the upper lobe not drained by the other major branch (figs. 16, 17).

Case 3

Clinical History. This female Negro child was admitted to Babies Hospital on August 24, 1955, when 6 weeks old for wheezing since the age of 2 weeks. The patient was born without difficulty after an uneventful 9-month pregnancy. The neonatal period was normal until 2 weeks of age. At that time, the parents noted slight wheezing, particularly when the patient was lying on her abdomen. About 2 weeks later, a slight cough developed in the morning. She was taken to a pediatrician who, upon radiographic examination, noted "right upper lobe atelectasis."

FIG. 19. Case 2. The largest of the accessory pulmonary arteries (*XPA*, injected in black) from the aorta is shown entering the lung from the periphery of the inferior margin. As the bronchi are approached, the branches of the artery become recurved, proceeding laterally in close relationship with the bronchi, as is typical of pulmonary arteries. They approximate the bronchi in size and taper with them toward the periphery.

There was no cyanosis or retraction and the cough and wheezing remained essentially unchanged. On admission, physical examination revealed an alert, active baby in no distress. The left anterior chest appeared to protrude, but both sides were resonant to percussion. Breath sounds were markedly decreased in the right upper lung field. No rales were heard. The heart sounds were strong and there were no murmurs. The blood count and urinalysis were normal. Fluoroscopic examination showed a mediastinal shift to the right, and the diagnosis of congenital hypoplasia of the right lung was made. Absence of the right pulmonary artery was queried. Upon reviewing the plain roentgenogram there was seen a separate right paracardiac shadow that represents the anomalous pulmonary vein (fig. 20). A tracheobronchogram showed a generally small caliber of the right bronchial tree with a "cavity" in the position usually occupied by the right middle lobe (fig. 21). The impression was that there was hypoplasia of the right middle lobe. Exploratory thoracotomy was considered not to be indicated at the time. The patient was discharged to have an angiocardiogram at a later date.

The second admission was on September 25, 1955, at 3 months of age for further study. In the interval, the child had had cough or stridor only on crying and there had been no cyanosis. An esophagram was normal. An angiocardiogram was interpreted as

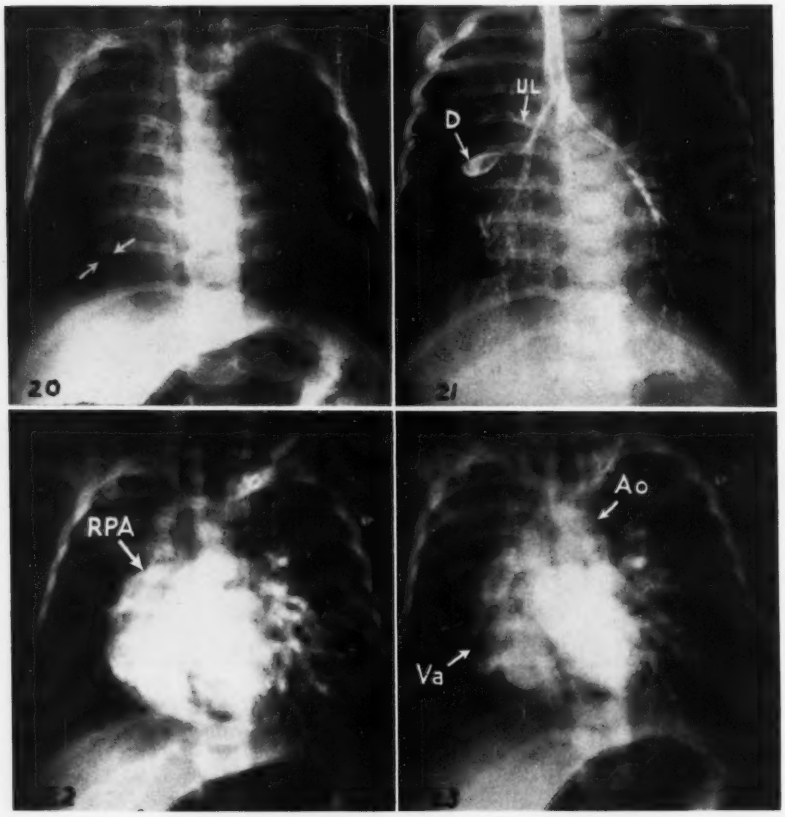


FIG. 20. Case 3. Plain film. The scimitar-shaped anomalous vein (arrows) is more or less parallel to the right border of the enlarged and dextroposed heart.

FIG. 21. Case 3. Bronchogram. The branches of the hypoplastic right upper lobe bronchus (*UL*) are visible (compare with fig. 25). The large aneurysmal outpouching of the lateral segmental bronchus (*D*) of the right middle lobe is filled with contrast medium. The branches of this bronchus peripheral to the sac are seen to possess the usual caliber, as if uninterrupted (compare with fig. 24).

FIG. 22. Case 3. Angiogram. At 5.4 sec., the small right pulmonary artery (*RPA*) and the enlarged trunk of the pulmonary artery and right ventricular chamber are opacified at the time when the cavity of the left ventricle has already received the contrast medium.

FIG. 23. Case 3. Angiogram. 6.5 sec. Opacification of the pulmonary vessels and right heart persist even after the aorta (*Ao*) has become outlined. The anomalous vein (*Va*) can now be clearly seen.

showing hypovascularization of the right lung consequent to congenital hypoplasia of the arteries. The main pulmonary artery and right and left branches were seen, but it was thought that most of the blood was carried through the left lung. The sequence of hemodynamic events was traced in a review of the angiograms (figs. 22, 23). At 3.2 sec., the right ventricle and left pulmonary artery were opacified, but there was only initial filling of the right pulmonary artery. At 5.4 sec., not only the pulmonary arteries, but also the veins, were visible, including the distal end of an anomalous right pulmonary vein. The aorta became opacified at 6.5 sec., but there was still evidence of recirculation through the right side of the heart, which persisted to 8.7 sec., but faded thereafter.

The third admission was on November 30, 1955. Wheezing had persisted at home. Two weeks prior to admission, she had an upper respiratory infection for which she was treated with penicillin. Feeding and weight gain had continued to be good.

At physical examination the temperature was 98.6 F., pulse 94, and respirations between 22 and 40. The patient was well developed and well nourished, active, and in no distress. The head was normal. There was a moderate preponderance of the left

anterior chest. The heart sounds were of good quality and were heard on both sides of the sternum. There were no murmurs. A biphasic wheeze was heard throughout the chest and there were no rales. The breath sounds were heard equally well in both lung fields. There was a large reducible umbilical hernia which protruded 4 cm., and had a circumference of 6 cm. The liver and spleen were not palpable.

It was thought that the congenital anomaly of the lung would jeopardize the patient's future. Since repeated upper respiratory infections were beginning to occur, it was thought that surgery was indicated. The patient underwent a right pneumonectomy on December 2, 1955. At operation the right pulmonary veins drained into the inferior vana cava. The right middle lobe and right lower lobe received arterial blood from the abdominal aorta, entirely or in part. A systemic artery to the upper portion of the lower lobe which arose from the thoracic aorta curved around and compressed the esophagus. The right pulmonary artery was seen to supply at least the small upper lobe and a portion of the middle lobe. There was herniation of a portion of the right lower lobe through the foramen of Bochdalek.

On the sixth postoperative day, roentgenographic examination revealed a normal left lung. There was the expected mediastinal shift to the right. The left lung field was still clear, and she was eating well.

On December 16, the fourteenth postoperative day, the patient was noted to be breathing with some degree of laryngeal obstruction. During examination, she became apneic and cyanotic. She responded to oxygen and artificial respiration and was placed in a croupette. In view of the possibility that this episode might be related to distortion of the left main bronchus secondary to a marked mediastinal shift, a right pneumothorax was performed by the injection of 50 ml. of air into the right pleural space over a period of 20 min. After this, aeration seemed better, but there remained a large laryngeal obstructive component.

Roentgenograms then revealed that the heart was shifted back to its preoperative position. There was a questionable infiltrate in the left upper lobe. A murmur was noted to the left of the sternum during the morning. During pharyngeal suction, she developed marked respiratory distress characterized by an epileptiform seizure with a tonic spasm of her chest and apnea. Artificial respiration was maintained by an endotracheal tube, but it was not possible to achieve good exchange. A tracheotomy was done, but the child's heart beat had ceased.

At necropsy, the most significant lesion was massive mediastinal emphysema. There was also a small subdiaphragmatic abscess. No significant changes were noted in the left lung except for edema. The liver had a large caudate lobe. An adrenal rest was found in the right kidney. The left kidney was somewhat misshapen.

Anatomic Observations. The right lung measured 11 cm. from apex to base and 8 cm. from the rounded posterior border to the sharp anterior margin. On the lateral aspect, 2 fissures were seen to delimit the boundaries of 3 lobes. There was an oblique fissure that lay somewhat more posteriorly than usual and demarcated a rather small lower lobe from the remainder of the parenchyma. The second fissure was shorter than the first, and was not transverse, but rather slanted upwards as well as anteriorly from its origin in the major oblique fissure. As a consequence, the "upper lobe" was much larger than usual, comprising approximately one third of the total mass of pulmonary substance. This appearance suggested that parenchyma ordinarily aerated from the right upper lobe bronchus was supplied by branches of the middle lobe bronchus.

On the hilar aspect, the large size of the middle lobe was especially obvious. The bronchial stump was rather high in the hilum. An almost transverse keel could be seen within the bronchial trunk, which measured only approximately 3 mm. from the level of transection to the level of the first subdivision. This keel divided the trunk into an "upper lobe" branch and the common trunk of the "middle" and "lower" lobes.

The single trunk of the transected pulmonary artery lay anterior to the bronchus.

A single large vein emerged on the medial aspect at the angle of junction of the middle and lower lobes in a position low and rather anterior even in comparison with that of the lower lobe vein in the normal lung.

Five "accessory pulmonary arteries" were present; all were on the medial and posterior aspects of the lung and were said to have taken origin in the subdiaphragmatic portion of the aorta. For convenience in description, they were numbered in a clockwise manner, beginning with number 1, a small artery that entered just below the main bronchus. Number 2 was a large vessel entering along the posterior margin halfway between the bronchial stump and the diaphragmatic margin. Just beneath this vessel was number 3, a smaller artery pursuing almost the same direction. Artery number 4 entered the lung, bending horizontally and forward, approximately 1 cm. above the diaphragmatic border. Artery number 5 was a large vessel that made an entrance in close relationship to the draining venous trunk, but just anterior to it. The arteries that it was possible to inject with black plastic comprise only numbers 2, 4, and 5.

The lung was the seat of interstitial emphysema, most marked on the lateral aspect of the lower lobe anteriorly. Most of the dissecting air could be seen within the pulmonary septa and beneath the pleura. Some air was apparently within the lymphatics.

A bronchovascular cast was prepared (figs. 24, 25). Roentgenograms of the cast demonstrated the anomalous distribution of the bronchi and the

FIG. 24. Case 3. Roentgenogram of cast (medial aspect). Lead sulfate was incorporated in the plastic to bring the bronchial tree into contrast. There is a large fusiform aneurysmal outpouching (*D*) of the lateral segmental bronchus of the middle lobe. The branches continue from this laterally in their usual caliber. The 3 rami of the upper lobe bronchus can be distinguished (B^1 = apical; B^3a = superior ramus of posterior segmental; B^3b = inferior ramus of posterior segmental). *ML* = middle lobe bronchus. *LL* = lower lobe bronchus.

FIG. 25. Case 3. Posteroanterior roentgenogram of cast. The 3 branches of the hyparterial right upper lobe bronchus are shown more clearly, and in relation to the upper lobe stem (*UL*). The medial (B^5) and lateral (B^4) branches of the middle lobe bronchus are also shown.

presence of an outpouching in the lateral ramus of the middle lobe bronchus that then yielded branches of normal size (compare figs. 21 and 24). These roentgenograms emphasized the bronchial distribution that was seen in relation to the vessels in the cast after digesting away the tissue (figs. 26, 27).

As suspected from the external appearance, the "upper lobe bronchus" had a distribution corresponding, somewhat irregularly, to the posterior and apical segments. The first branches of the upper lobe bronchus were not derived until 1 cm. from its origin. Here there was a division into B3a (superior ramus of posterior segment) and the common branch of B3b (inferior ramus of posterior segment) and B1 (apical segmental bronchus).

The common trunk of the "middle" and lower lobes had a length of 3 mm., before dividing into "middle" and lower lobar trunks.

The "middle lobe" bronchus, after a course of 5 mm., divided into medial and lateral branches. The medial was much larger. It yielded 2 successive branches that aerated the region of the anterior segment. Three millimeters beyond the origin of the lateral segmental bronchus there was a fusiform aneurysmal outpouching 1.2 cm. long and approximately 4 mm. in diameter.

The lower lobe bronchus was 8 mm. long. No superior segmental bronchus was derived from this trunk. The first branch was the medial segmental; below this was the common basal trunk which had a length of 1.4 cm. before dividing into B8 (anterior segmental) and the common trunk of B9 (lateral segmental) and B10 (posterior segmental). Accessary subsuperior bronchi were yielded by this common trunk, and also as posterior branches of all of the basal bronchi.

The trunk of the pulmonary artery divided into an upper lobe branch and a common trunk that supplied the remainder of the lung. The upper lobe branch divided after a course of 3 mm. into branches that corresponded exactly to those of the major bronchi as described for this lobe.

The common trunk within 2 mm. of its origin yielded a small artery that supplied most of B4 (lateral segment of middle lobe), then, after a course of 1.2 cm., it yielded a large branch to B5 (medial segment), which supplied also those branches that represent the B2 (anterior) segment of the normal lung. There was a third, minute artery derived from a short common trunk with a B8 branch that supplied the medial rami of B4. The common basal branches otherwise followed the bronchial pattern closely.

The anomalous arteries derived from aorta were given the same numerical designations used in the external description of the specimen. Artery number 1 (not injected) may, in fact, have been a bronchial artery, since there appeared to be no bronchial distribution devoid of true pulmonary arterial supply in the region of its entrance into the lung.

FIG. 26. Case 3. Cast. Medial aspect, comparable to figure 24. The relations of the bronchi and vascular structures are demonstrated. The trunk of the large anomalous draining vein is seen at the confluence of its major tributaries. Three of the accessory pulmonary arteries are labeled in accordance with the text. *B* = bronchus; B^1 = apical segmental bronchus of upper lobe; B^3b = inferior ramus of posterior segmental bronchus, upper lobe; *D* = "diverticulum" of lateral segmental bronchus of middle lobe; *A* = artery; *XPA* = "accessory pulmonary artery" from aorta; *Va* = vein; *UL* = upper lobe; *ML* = middle lobe; *LL* = lower lobe.

tery number 2 supplied portions of B5, as did mber 3. The distribution of the latter was pre- mptive, since number 3 was not injected. Artery mber 4 was injected and supplied distal portions B7 and B8. Artery number 5 supplied a part of the segment. Arteries number 2 through 5, all de- ed from the subdiaphragmatic portion of the aorta, had the characteristic distribution of pulmonary arteries. The course of each was not plexiform, but instead followed the branchings of the bronchial ramus. They were end arteries, in the same sense as the pulmonary arteries, and their size in relation to the bronchus was similar. There was no evidence that they yielded any blood supply to the bronchial

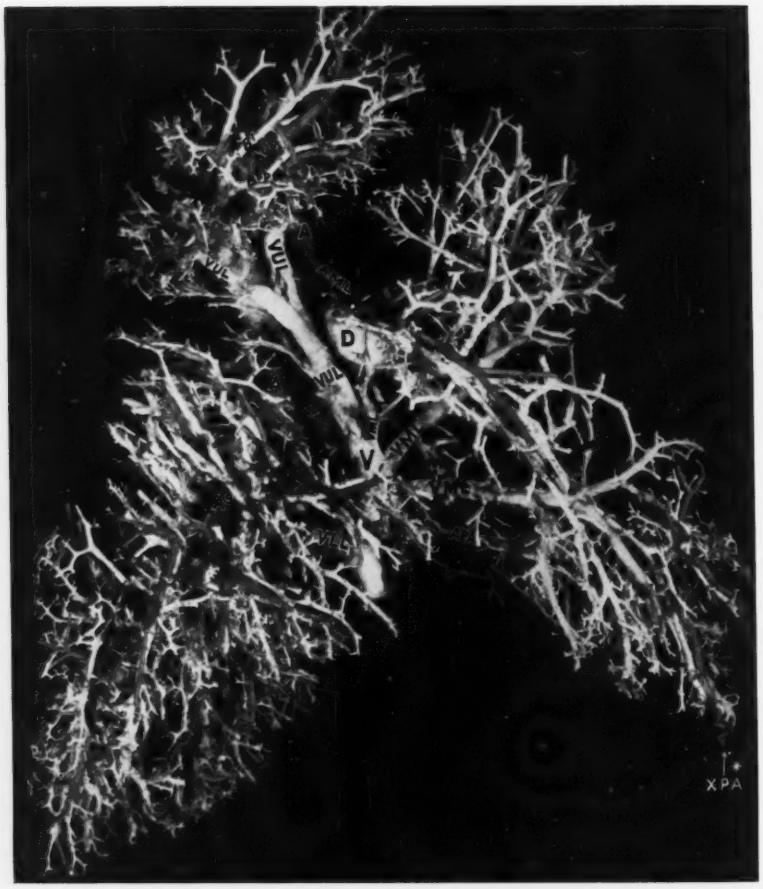


FIG. 27. In a lateral view of the cast, 2 branches of the upper lobe bronchus can be seen. The courses of the major venous trunks are displayed. At the termination of one of the accessory pulmonary arteries (indicated by an asterisk) the vessel assumes a pigtail tortuosity, characteristic of pulmonary arteries carrying blood at excessively high pressure. (Key as in fig. 26).

tree until the alveolated portions were reached. Their distal branches (fig. 27) were marked by a "pigtail" tortuosity characteristic of high pressure, as seen in the pulmonary arteries in most instances of transposition of the great vessels.

The single large vein was formed by the confluence of many branches resembling a candelabrum. There were 2 main trunks: an anterior trunk passed obliquely upwards and laterally to drain the upper and middle lobes; the other trunk drained the lower lobe and was formed by the union of a vessel, V7, that served chiefly the medial segment, with the common trunk draining the basal segments. Portions of adjacent segments were, of course, drained by these vessels, as is characteristic of pulmonary veins in general. Several minute branches also entered the various trunks close to their confluence.

Two blocks of tissue were taken from each of the 3 lobes for microscopic sections. In the alveoli, there were occasional large mononuclear cells. There was dissection of the interstitial connective tissue by gas. Focal hemorrhage was present within many of the alveoli, and some contained fibrin. In one margin there was apparent necrosis of the alveoli, interpreted to be the result of clamping during operative removal. This also was thought to account for the hemorrhage and fibrinous material within the alveoli. There were no changes suggestive of an organizing pneumonitis in the sections studied. A few bronchioles that were present had well-preserved epithelium, despite the injection procedure.

SUMMARY

Observations upon 3 instances of anomalous pulmonary venous return into the inferior

vena cava are presented in comparison with previously published material. This lesion is often asymptomatic and compatible with long life, but is sometimes associated with shortness of breath and symptoms of chronic bronchopulmonary disease. In those patients subjected to the most detailed study, there were often found additional anomalies of bronchial distribution (such as the presence of a mirror image of the left lung on the right side, or cystic diverticula of the bronchial tree), and accessory pulmonary arteries from the descending thoracic aorta. Bronchographic and angiographic technics are useful in bringing such associated anomalies to light. These features should be considered with reference to the usefulness of the right lung and its freedom from chronic suppurative disease in planning corrective or extirpative surgery.

Summario in Interlingua

Es presentate—e comparate con previemente publicate materiales—observationes colligite in 3 casos de anomale retorno pulmonovenose verso le vena cave inferior. Le lesion es frequentemente asymptomatic e non incompatible con longevitate, sed a vices illo es associate con dyspnea e symptomas de chronic morbo bronchopulmonar. In le patientes in qui le plus detaliate studios esseva executate, il esseva frequentemente possibile constatar anomalias additional de distribution bronchial (per exemplo le presentia al latere dextere de un imagine specular del pulmone sinistre o cystic diverticulos del arbore bronchial) e accessori arterias pulmonar exiente ab le descendente aorta thoracic. Technicas bronchoe angiographic es utile in le detection de tal associate anomalias. In elaborar planos pro chirurgia corrective o extirpative, le mentionate punctos deberea esser considerate con referentia al utilitate del pulmone dextere e a su libertate ab chronic morbo suppurative.

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As an animal Body consists not only of a wonderful texture of solid Parts, but also of a large proportion of Fluids, which are continually circulating and flowing, thro' an inimitable Embroidery of Blood-Vessels, and other inconceivably minute Canals: And as the healthy State of an Animal principally consists, in the maintaining of a due Equilibrium between those Solids and Fluids; it has, ever since the important Discovery of the Circulation of the Blood, been looked upon as a Matter well worth the enquiring into, to find the Force and Velocity with which these Fluids are impelled; as a likely means to give a considerable Insight into the animal Economy.—REVEREND STEPHEN HALES, B.D., F.R.S. From the Introduction of: *Statical Essays.* Vol. II, London, 1733.

Diagnosis of Mitral Regurgitation by Cardioangiography

By PHILIP W. SMITH, M.D., HUGH A. CREGG, M.D., AND KARL P. KLASSEN, M.D.

To determine the feasibility of demonstrating mitral regurgitation by injection of contrast media into the left ventricle, percutaneous and subxiphoid left ventricular punctures were carried out in dogs and subsequently in human beings. Contrast media were injected and roentgenographic studies made. The correlation between the roentgenographic and subsequent anatomic findings at operation or autopsy is emphasized. The method appears to be relatively safe if proper safeguards are observed. The results indicate that the method is of value in determining the competence of the mitral valve and relative degree of insufficiency.

THE surgical treatment of pure mitral stenosis has proved a sound procedure for the relief of the symptoms produced by rheumatic valvular disease. However, mitral insufficiency still presents a serious problem in its management and no adequate surgical procedures are available for the correction of this condition at the present time. Until an adequate method has been evolved for the correction of mitral insufficiency, a more accurate method should be available for the preoperative differentiation of mitral insufficiency and stenosis. A large number of patients are undergoing exploratory thoracotomy and cardiotomy with a diagnosis of mitral stenosis who are found to have predominate insufficiency; on the other hand, an operation that might benefit patients with mitral stenosis is being withheld on the basis of various clinical impressions that would indicate the presence of mitral insufficiency.

If satisfactory operations are developed for the correction of mitral regurgitation, a clinical method that gives accurate preoperative information concerning the function of the mitral valve will still be desirable. Any method that provides a more accurate preoperative diagnosis should reduce operative mortality and morbidity. Moreover, objective follow-up of patients after surgery demands accurate evaluation of this important function of the valve.

Recent attempts have been made to determine the degree of mitral insufficiency and stenosis by the use of angiocardiography. Because of the large size of the left atrium in patients with mitral disease, however, contrast dilution and retention in this chamber ordinarily prevents adequate visualization of the atrial reflux during systole. The limitations of angiocardiography in evaluating lesions of the mitral valve have been well outlined by Soloff and associates.[1] The shortcomings of other presently advocated clinical methods to assess mitral regurgitation have recently been discussed by Radner.[2] The importance of having such a method available has been stressed by Kent and co-workers.[3]

Selective angiocardiography and cardioangiography as practiced by Kjellberg[4] and Lind[5] have been shown to be of great diagnostic value in congenital heart disease. These investigators injected contrast media into the great vessels and various chambers of the heart through an intravascular catheter extending from one of the extremities to the heart.

More recently, Björk[6] injected contrast media through a needle inserted into the left atrium from the back and made rapid serial x-ray exposures to study the mitral valve. In a case of mitral regurgitation it was possible to demonstrate lack of closure of the valve cusps during ventricular systole. The size of the needle was limited because of the tendency

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Aided by a Grant from the Central Ohio Heart Association.

Paper presented at the meeting of the American Heart Association, October 22, 1955, New Orleans, La. Abstracted, Circulation **12:** 777, 1955.

for the punctured atrium to bleed. He did not recommend this procedure for clinical use.

Materials and Method

Percutaneous puncture of the right or left ventricle of the heart with the introduction of contrast media has been reported previously.[7-9] The injection equipment consists of a 5½-inch, 15-gage short-beveled needle attached to a 30 ml. syringe containing 20 to 30 ml. of 70 per cent Diodrast. The patient is placed supine on the x-ray table and the left side raised obliquely 50 to 90 degrees, so that the left ventricle clears the spine in the radiograph. Under local anesthesia a subxiphoid puncture of the left ventricle is accomplished. Left ventricular pressures are recorded and rapid manual injection of the contrast medium is made. Serial 2/sec. radiographs are taken with the Fairchild camera during the period just following this injection.

The details of this method and its dangers and safeguards have been reported previously[9]. In the original study it was noted that contrast media did not regurgitate through a competent mitral valve in the dog. This observation was verified again at this time by carrying out an acute experiment in 2 additional dogs.

With positive pressure intratracheal anesthesia and open thoracotomy the dog's heart was exposed. Pressures were obtained in the left atrium simultaneously with the electrocardiogram. A 17-gage needle was then inserted into the left ventricle through the subxiphoid approach and 10 ml. of 70 per cent Diodrast was rapidly injected. Radiographs at 2/sec. were obtained during injection. A competent mitral valve was demonstrated (fig. 1), none of the contrast medium appearing in the left atrium.

By a blind technic the mitral valve was then injured to permit mitral regurgitation. Leakage of the valve was evidenced by the appearance of a thrill over the left atrium and a rise in the left atrial pressure with a characteristic change in the left atrial pressure curve. The left ventricular injection was then repeated and marked regurgitation of the contrast medium resulted through the mitral valve (fig. 2) with opacification of the left atrium and the adjacent pulmonary veins. This dog was sacrificed and the heart examined to determine the extent of the injury to the mitral valve. An 8 mm. laceration was present in the free edge of the septal cusp about 1 cm. from the posteromedial commissure.

The same procedure was carried out in a second dog but the mitral valve was less extensively injured. Here a 2 mm. laceration of the free edge of the posterior portion of the mural cusp was produced. Cardioangiography revealed a competent valve before laceration and moderate regurgitation through the lacerated incompetent valve.

The observance of mitral regurgitation by percutaneous cardioangiography has been reported previously.[10, 11] Any degree of opacification in the

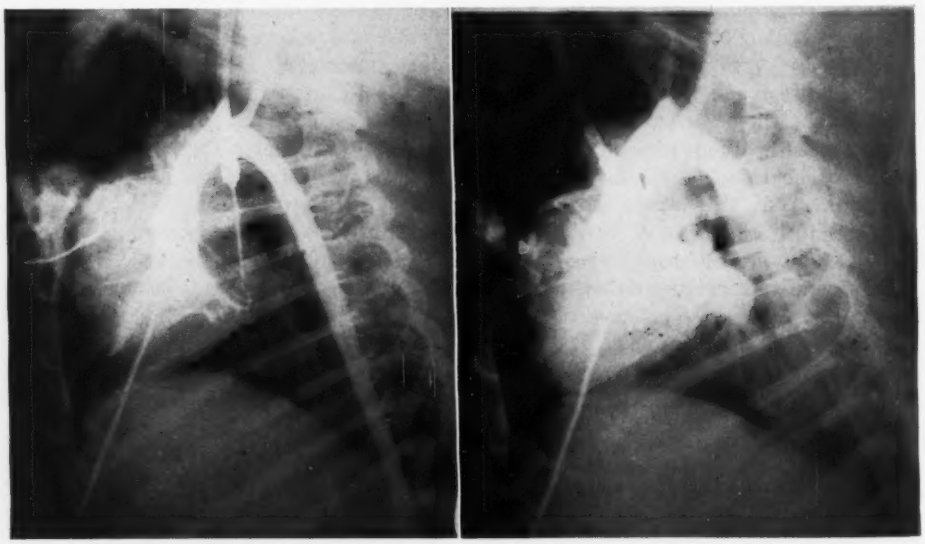

Fig. 1 and 2. *Left.* Normal cardioangiogram in dog. Competent mitral valve demonstrated by absence of opacification of left atrium. The small needle is in the left atrium for pressure determination and the large needle is in the left ventricle for the injection of the Diodrast. *Right.* Cardioangiogram in same dog after surgical laceration of the mitral valve. Note the severe regurgitation into the left atrium and the pulmonary veins.

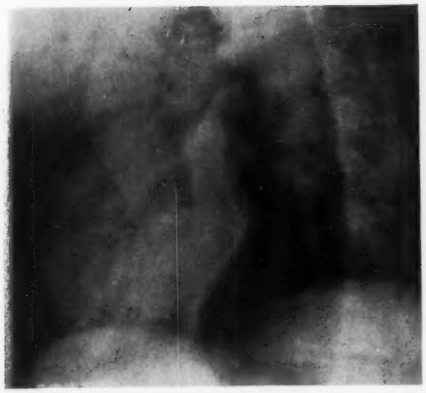

FIG. 3. Intravenous angiocardiogram in the left anterior oblique projection in a patient with a normal mitral valve. Contrast medium can be seen in the left atrium, the left ventricle, and the aorta. Note the relationship of the left atrium to the aorta and the left main-stem bronchus.

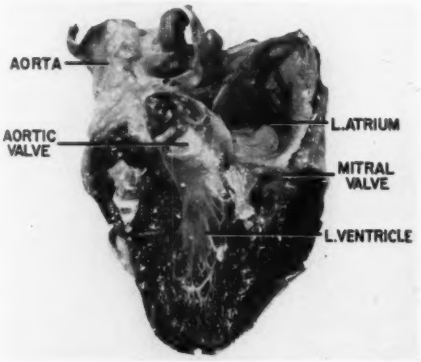

FIG. 4. A sagittal section through the mitral and aortic valves of the normal human heart in the left anterior oblique plane demonstrates the position of the left atrium in relation to the mitral valve, the aorta, and the aortic valve. Note the relationship of the septal cusp of the mitral valve to the aortic outflow tract.

region of the left atrium immediately after left ventricular injection is considered evidence of mitral regurgitation. The amount of insufficiency may be estimated by the degree of atrial opacification provided other variables are taken into account. These variables include the quality of the films, the size of the left ventricle and the left atrium, the amount and density of the contrast medium injected, and the length of time of the injection.

To interpret correctly the radiographs obtained by this method it is important to know the anatomic relationships of the mitral valve in the left anterior oblique projection (actually the right posterior oblique projection). Figure 3 represents a conventional angiocardiogram taken with the patient in this position. In this thin adult, 50 ml. of 70 per cent Diodrast was injected rapidly intravenously and serial radiographs were taken. This radiograph was chosen from the series because it best demonstrates the relationships of the mitral valve in the left anterior oblique (right posterior oblique) view.

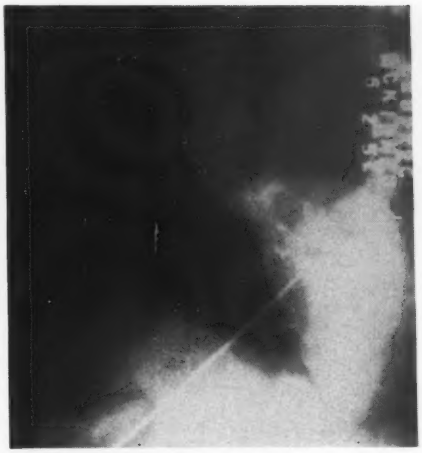

FIG. 5. Cardioangiogram of C. Mc. Competent mitral valve in patient with mitral stenosis. Note the lack of opacification in the region of the left atrium.

A normal human heart was removed at autopsy, and the chambers were filled with paraffin wax to prevent their collapse during sectioning. Sagittal sections were made in the left anterior oblique plane. A sagittal section in this plane through the mitral and aortic valves demonstrates the relationships between the atrial chamber, the mitral valve, the ventricular cavity, the ventricular out-flow tract, and the aortic valve (fig. 4).

The mitral valve was studied in 20 cases undergoing cardioangiography.

RESULTS

In 10 of the 20 cases the mitral valve was found at cardioangiography to be entirely competent (fig. 5). In these cases no opacification was seen in the region of the left atrium in any of the serial radiographs. An important landmark in this right posterior oblique projection is the left main-stem bronchus, which should mark the superior border of the left atrium.

The opportunity to check the competence of the mitral valve anatomically in these 10 patients has thus far presented itself twice. One patient died because of degeneration of a homo-

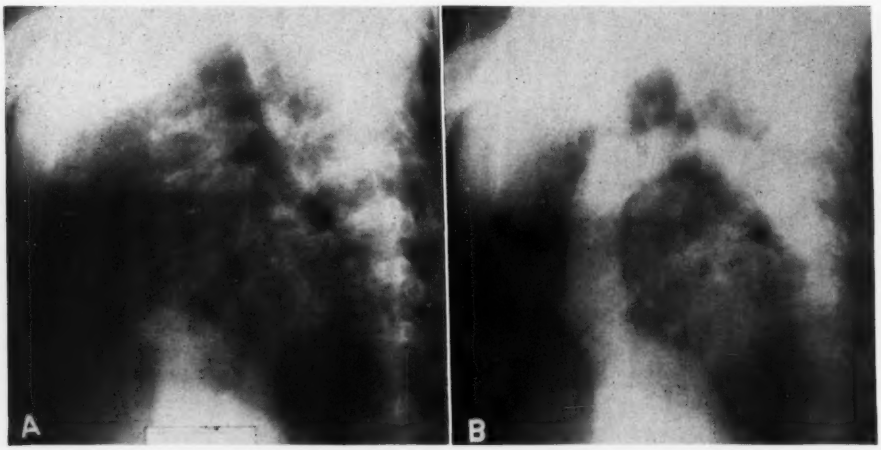

FIG. 6. Cardioangiogram of R. C. Minimal (1 plus) regurgitation through the mitral valve. *A*. Ventricle beginning to fill with contrast medium. *B*. Later film in series showing minimal opacification in region of left atrium (compare with *A*).

graft inserted for correction of coarctation of the aorta. A resulting dissecting aneurysm finally ruptured 1 year after cardioangiography and 2 years after the placing of the graft. At autopsy, the mitral valve leaflets were normal and there was no dilatation of the valve ring. This valve was competent, confirming the previous cardioangiographic findings.

In the second case the cardioangiographic findings were not in agreement with the subsequent operative report. A competent mitral valve was apparent in the cardioangiogram; yet the operating surgeon recorded 2-plus mitral regurgitation in addition to the mitral stenosis that was present. The reason for this discrepancy is not yet certain, but it represents the only case encountered thus far of the disparity between the anatomic findings and the cardioangiograms.

In 10 cases, mitral regurgitation of varying degree was demonstrated. The amount of regurgitation has been estimated radiographically on the basis of the relative degree of opacification in the region of the left atrium. In films of good quality the slightest increase in opacification of the left atrial chamber is considered significant.

The relative size of the left atrial chamber is important in assessing the significance of its opacification by this method. Thus, slight

FIG. 7. Cardioangiogram of F. W. Three-plus mitral regurgitation. Note the huge size of the left ventricle and the left atrium.

opacification of a large left atrium may indicate just as severe mitral regurgitation as a more marked opacification of a smaller chamber. The method is not quantitatively accurate, but with experience in interpretation one should be able to quantitate the degree of regurgitation roughly as 0, 1, 2, 3, or 4 plus. This is probably adequate for most clinical purposes.

Some estimate of the size of the left ventricle

FIG. 8. Photograph of mitral valve (from atrial side) of F. W. Patient died of her disease 8 months after the radiograph demonstrated in figure 7 was obtained. The open fixed mitral orifice measured 2 by 1 cm.

may also be possible and may be of assistance in diagnosis. Knowledge of the exact time in the cardiac cycle represented on the radiographs, i.e., systole or diastole, would be of value in this regard. Coupling of the x-ray exposures with the electrocardiograph has not been done in this series of cases, however. Other refinements of the method are possible, but the advantage of simplicity is also self-evident.

Figure 6 is a cardioangiogram interpreted as showing 1-plus mitral regurgitation. Definite but minimal opacification is seen in a relatively small left atrium (compare fig. 6*A* and *B*). At operation after digital atrial exploration, the surgeon estimated mitral regurgitation as 1 plus.

In a 47-year-old white woman with far-advanced rheumatic heart disease, functional class IV, the cardioangiogram (fig. 7) was interpreted as showing 3-plus mitral regurgitation. At autopsy, 8 months later, a fixed 2 by 1 cm. opening of the mitral valve (fig. 8) was found. The valve edges were markedly thickened and sclerotic, with some calcification

FIG. 9. Cardioangiogram of P. F. Four-plus mitral regurgitation with aneurysmal dilatation of the left atrial appendage and without appreciable enlargement of the atrium proper (30 ml. of 90 per cent Hypaque injected in this case).

anteriorly. The chordae tendineae were thickened and shortened. This deformed mitral valve permitted marked regurgitation during life. The left atrium was huge; there were also hypertrophy and dilatation of the left ventricle, moderate aortic stenosis, and hypertrophy and dilatation of the right ventricle and right atrium with functional tricuspid insufficiency.

In another patient with a clinical diagnosis of mitral regurgitation, the routine radiographic studies of the chest, including a lateral with a barium swallow, failed to reveal any enlargement of the left atrium. Cardioangiography (fig. 9) revealed marked mitral regurgitation with an aneurysmal dilatation of the left atrial appendage without significant enlargement of the atrium proper.

Of the 10 cases showing some degree of mitral regurgitation by cardioangiography, then, the valves were explored surgically in 3, and a fourth patient came to autopsy. The interpretation of the cardioangiograms, as to the approximate degree of mitral regurgitation, was found to correlate correctly with the anatomic findings in all 4 cases.

Discussion

Cardioangiography is a procedure that can be accomplished simply and with relative safety. Thirty-one ventricular punctures have been performed in 30 patients with no mortality. Ponsdomenech and Nunez[8] reported 56 ventricular punctures without mortality. In the second case of the authors' present series there was a significant morbidity. This case, reported previously,[9] developed ventricular arrest following the injection of contrast medium almost directly into the ostium of the left coronary artery as a result of malposition of the needle tip. Thoracotomy and cardiac massage were required and the patient recovered. He died several months later, however, from a ruptured aneurysm of the thoracic aorta. Autopsy revealed no evidence of the previous cardiac puncture.

The competence or relative degree of incompetence of the mitral valve can be readily assessed by cardioangiography. No other method presently available appears to be as accurate in evaluating this important function of the mitral valve.

Anatomic evidence is available for comparison in 6 of the 20 cases studied in this series. In 5 of these 6 cases there is essential agreement relative to the competence of the mitral valve between the cardioangiographic findings and the subsequent anatomic findings at operation or autopsy. Obviously a much larger series of cases is needed before any final conclusions can be drawn.

Summary

Percutaneous puncture of the left ventricle with the injection of contrast medium has been utilized in dogs to depict radiographically the state of competence of the mitral valve. The competent valve before injury and the incompetent valve after surgical laceration of the mitral leaflet has been demonstrated.

Thirty-one ventricular punctures in 30 patients have been carried out without mortality. Twenty of these patients have been studied relative to the state of competence of the mitral valve. The cardioangiograms in 10 patients were interpreted as showing a competent mitral valve and in 10 patients as showing varying degrees of regurgitation.

The correlation between the cardioangiographic findings and subsequent anatomic findings at operation or autopsy has been stressed. It is believed that this method holds promise for determining the presence or absence of mitral regurgitation, and its approximate degree when present.

Addendum

Since submitting this paper for publication, 2 additional patients have had cardioangiograms and have subsequently come to operation. The findings at cardioangiography of a competent mitral valve in 1 and a very minimal degree of mitral regurgitation in the other were in precise agreement with the operative findings.

Summario in Interlingua

Punction percutanee del ventriculo sinistre con injection de substantia de contrasto ha essite usate in canes pro establir radiographicamente le stato de competentia del valvula mitral. Esseva demonstrate le valvula in stato

competente ante su vulneration e in stato ncompetente post laceration chirurgic del olietto mitral.

Trenta-un punctiones ventricular in 30 pa-ientes ha essite executate sin mortalitate. Vinti del patientes esseva studiate in re le stato de competentia de lor valvulas mitral. In 10 patientes le cardioangiogrammas esseva in-terpretate como reflectente competentia del valvula mitral; in le altere 10, illos pareva indicar varie grados de regurgitation.

Es sublineate le correlation inter le consta-tationes cardioangiographic e le subsequente constatationes anatomic al operation o al necropsia. Nos opina que iste methodo es promittente como adjuta in le determination del presentia o absentia de regurgitation mitral e del grado approximative que illo ha attingite.

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Lawrence, G. H., Zimmerman, H. B., Bercu, B. A., and Burford, T. H.: Evaluation of Mitral and Aortic Valvular Disease by Left Heart Catheterization. Surg. Gynec. & Obst. **101:** 558 (Nov.), 1955.

The authors described a method of performing left atrial catheterization for evaluation of patients for cardiac surgery. The study was done on 25 patients without any untoward effects.

The first step consisted of placing a metal marker over the position of the left atrium while the patient was being fluoroscoped. This location was then marked on the skin with ink. Next, a 17-gage, 15 cm. needle was introduced through this site, directed anteromedially at an angle of 20 degrees with the vertebral column. After the tip passed through the subcutaneous tissue, the obturator was removed and the needle was then inserted into the atrium. A no. 442-T polythene catheter was threaded through the needle into the atrium and ventricle.

The authors believe that their experience justifies the application of left heart catheterization to the objective estimation of the physiologic effects of mitral and aortic valvular lesions.

Abramson

Blood Coagulation After a Fat Meal

By Ratko Buzina, M.D., and Ancel Keys, Ph.D.

The influence of meals on the coagulability of blood was studied in experiments on 20 men with parallel nonfed controls. The whole blood clotting time in siliconized tubes was not altered by a low-fat meal or by continued absence of a meal, but it was significantly shortened after a meal containing 100 Gm. of butterfat. The degree of lipemia did not determine the degree of shortening. There was no important effect on prothrombin time of the fatty meal as contrasted with the nonfatty meal or with no meal. Heparin tolerance results were difficult to interpret.

A VARIETY of in vitro experiments have indicated that lipids influence blood coagulation,[1-3] from which coagulability might be expected to increase in the lipemic period after a fatty meal. This was, indeed, reported by Waldron, Beidelman and Duncan,[4] but it was denied by Tulloch, Overman, and Wright.[5] However, the former group maintained their position on the basis of further experiments, with special attention to the avoidance of artifacts,[6, 7] and Fullerton, Davie, and Anastopulos[8] found that a fatty meal shortens the clotting time of recalcified plasma in the presence of snake venom. But Manning and Walford[9] sided with Tulloch, Overman, and Wright on the basis of tests with cream feeding and with a fatty breakfast.

This was the highly controversial picture when we began to examine the question with carefully controlled studies on physically healthy men aged 35 to 60 in a rigidly controlled metabolic unit in Hastings State Hospital.

Methods

Blood was withdrawn from an arm vein with siliconized syringes and no. 18-gage needles coated with Arquad 2 C. If there was any difficulty in obtaining blood, a new venepuncture was made with a new needle and syringe. A stopwatch was started as soon as blood entered the syringe. One milliliter of blood was added to each of 4 siliconized tubes in a water bath at 37 C., and 4.5 ml. of blood was added to 0.5 ml. of 0.1 M sodium oxalate; the latter mixture was centrifuged to provide oxalated plasma.

For whole blood clotting time, one of the siliconized tubes was tilted every 60 sec. until clotting occurred, at which time tilting of the second tube was similarly started. When clotting occurred in the second tube, tilting of the third and fourth tubes was started simultaneously, and the average clotting time (computed from the time of blood drawing) in these was taken as the final clotting time. The standard error of measurement (S.E.M.) between duplicates* proved to be ±1.608 min. with 100 samples.

Prothrombin time was estimated at 37 C. in 12.5 per cent oxalated plasma (diluted with 0.85 per cent NaCl solution). To 0.1 ml. of this diluted plasma, was added 0.1 ml. of Difco thromboplastin and then, after a few seconds, 0.1 ml. of 0.02 M calcium chloride was added and the stopwatch was started. S.E.M. was ±1.041 sec. in 132 samples.

The heparin tolerance test was done with oxalated blood at 37 C. by a modification of the method of Sigg.[10] To 0.15 ml. of oxalated whole blood was added 0.15 ml. of fortieth-molar calcium chloride containing 0.56 units of heparin.† The test was made in duplicate tubes that were tilted every 60 sec. S.E.M. was ±2.108 min. in 100 samples.

All studies were started in the morning, with the subjects in the fasting, resting state. After drawing the control blood samples, a "meal" (1080 calories) consisting of 300 ml. of 40 per cent butterfat cream was ingested and then, as the subjects continued to rest, further blood samples were taken at 1.0, 2.5, 4.0, and 5.5 hours from the time of the meal.

Finally, to distinguish between effects of fatty meals as contrasted with low-fat meals, the experiments were repeated with the same subjects with a meal that provided 940 calories but only 0.3 Gm. of fat. This low-fat meal consisted of rice, sugar, and "divinity" candy and contained 18 Gm. of protein. The result was a series of precisely parallel values for the effect of a fatty meal (F), for the nonfat control meal (C_1), and for a fasting control (C_2).

Results

The results of experiments on 20 subjects are summarized in table 1 and the statistical analysis is given in table 2. The whole blood

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The work reported here was made possible by research grants from the Schweppe Foundation, Chicago, by the National Dairy Council, Chicago, and by the Minnesota Heart Association.

* Computed as S.E.M. = $\sqrt{\Sigma\Delta^2/2N}$.

† Testagar and Co., Detroit, Mich.

TABLE 1.—*Effect of a Fat Meal on Blood Coagulation*

Group	Item	Time in hours			
		1	2.5	4	5.5
F	Whole blood, mean	0.95	4.25	3.95	5.50
F	S.E.	±1.217	±1.237	±0.904	±1.160
C_1	Whole blood, mean	−2.92	−1.78	−1.71	−1.92
C_1	S.E.	±1.179	±0.846	±1.273	±1.616
C_2	Whole blood, mean	−0.94	−1.83	−1.22	−1.28
C_2	S.E.	±0.756	±1.299	±1.074	±0.921
F	Prothrombin, mean	3.60	3.85	1.60	2.75
F	S.E.	±0.653	±0.924	±0.998	±1.289
C_1	Prothrombin, mean	1.42	1.07	1.78	4.00
C_1	S.E.	±0.775	±1.014	±1.392	±0.961
C_2	Prothrombin, mean	2.44	1.89	2.22	1.94
C_2	S.E.	±0.754	±1.038	±1.144	±1.478
F	Heparin, mean	0.10	0.70	−0.45	−1.70
F	S.E.	±0.560	±0.729	±0.642	±0.858
C_1	Heparin, mean	−1.14	−3.07	−1.00	−2.28
C_1	S.E.	±0.762	±0.633	±0.688	±0.774
C_2	Heparin, mean	0.94	0.89	1.50	0.94
C_2	S.E.	±0.891	±0.718	±0.672	±0.501
F	Density, mean	0.0256	0.2688	0.3058	0.2734
F	S.E.	±0.0151	±0.0358	±0.0401	±0.0380
C_1	Density, mean	−0.0002	−0.0030	−0.0027	−0.0064
C_1	S.E.	±0.00272	±0.00272	±0.00278	±0.00320
C_2	Density, mean	−0.0015	0.0039	0.0040	−0.0032
C_2	S.E.	±0.00478	±0.00528	±0.00597	±0.00632

Twenty men received 300 ml. of 40 per cent cream (F) and 12 control men (C_1) received the same amount of calories derived from carbohydrates and proteins only. (C_2) = 18 control, unfed, men. Whole blood coagulation time shortening ("Whole Blood") is in minutes, prothrombin time shortening ("Prothrombin") is in seconds, heparin tolerance time ("Heparin") is in minutes. S.E. = standard error of the mean.

clotting time tended to be shortened in all 4 of the samples drawn after the fatty meal, though the average difference was slight in the sample drawn 1 hour after the meal. In contrast, both the low-fat meal (C_1) and the continued absence of a meal (C_2) tended to produce somewhat longer clotting times than were observed in the premeal sample. The net result for whole blood clotting is that there was a highly significant shortening related to the fatty meal at 2.5, 4, and 5.5 hours, the mean net shortening over this period being 6.57 min. with reference to a nonfat meal and 6.01 min. with reference to no meal. The mean net shortening at 1 hour after the fat meal is less impressive but this also seems to be real when comparison is made with both C_1 and C_2. In contrast, there was at no time a significant difference between the coagulation time after a nonfat meal as compared with no meal.

The prothrombin time after the fatty meal showed an average shortening that varied between 1.60 and 3.85 sec.; this is statistically significant with reference to the premeal value. However, both after a low-fat meal and after continued fasting there was also a tendency toward shorter prothrombin time, so that it is dubious whether the fatty meal has any specific effect on this variable.

The data from the heparin tolerance test are difficult to interpret. After the fatty meal there was some tendency toward a prolongation of the heparin effect, and this tendency was much more evident after a low-fat meal. In contrast, when no meal was fed, there was some trend toward a reduction in the duration of the heparin effect. The net result is a highly significant difference between the heparin tolerance during continued fasting and that after *any* meal, though the time relations may be affected by the type of meal.

The degree of lipemia, expressed as optical density, showed a slight increase after 1 hour following the ingestion of cream and a high

TABLE 2.—*Statistical Analysis of the Results in Table 1*

	Time in hours			
	1	2.5	4	5.5
Whole blood, mean diff., $F - C_1$	3.88	6.04	5.66	7.42
S.E. of diff.	±1.707	±1.644	±1.516	±1.934
t	2.272	3.672	3.736	3.840
Whole blood, mean diff., $F - C_2$	1.89	6.08	5.17	6.78
S.E. of diff.	±1.471	±1.794	±1.395	±1.503
t	1.285	3.389	3.706	4.511
Whole blood, mean diff., $C_1 - C_2$	−1.98	0.044	−0.494	−0.648
S.E. of diff.	±1.346	±1.658	±1.656	±1.764
t	1.477	0.0265	0.298	0.367
Prothrombin, mean diff., $F - C_1$	2.17	2.78	−0.18	1.25
S.E. of diff.	±1.005	±1.392	±1.666	±1.742
t	2.161	1.996	0.111	0.718
Prothrombin, mean diff., $F - C_2$	1.16	1.96	−0.62	0.81
S.E. diff.	±0.980	±1.139	±1.512	±1.952
t	1.184	1.415	0.410	0.415
Prothrombin, mean diff., $C_1 - C_2$	−1.012	−0.819	−0.435	2.06
S.E. of diff.	±1.088	±1.478	±1.786	±1.882
t	0.930	0.554	0.244	1.094
Heparin, mean diff., $F - C_1$	1.24	3.77	0.55	0.58
S.E. diff.	±0.941	±1.022	±0.960	±1.212
t	1.320	3.689	0.572	0.498
Heparin, mean diff., $F - C_2$	−0.84	−0.19	−1.95	−2.64
S.E. of diff.	±1.042	±1.027	±0.930	±1.025
t	0.806	0.185	2.096	2.580
Heparin, mean diff., $C_1 - C_2$	−2.082	−3.961	−2.50	−3.22
S.E. of diff.	±1.214	±0.988	±0.974	±0.886
t	1.715	4.009	2.566	3.634
Density, mean diff., $F - C_1$	0.0258	0.2718	0.3085	0.2798
S.E. of diff.	±0.0183	±0.0432	±0.0468	±0.0442
t	1.409	6.291	6.592	6.330
Density, mean diff., $F - C_2$	0.0271	0.2649	0.3018	0.2766
S.E. of diff.	±0.0166	±0.0380	±0.0427	±0.0405
t	1.633	6.959	7.059	6.826
Density, mean diff., $C_1 - C_2$	0.0013	−0.0069	−0.0067	−0.0032
S.E. of diff.	±0.00595	±0.0065	±0.0072	±0.0077
t	0.219	1.063	0.935	1.244

The pooled variances for the $F + C_1$ and C_2 groups are used to compute the standard errors of the differences between the means, $F - C_1$ and $F - C_2$. Abbreviations as in table 1. The following probabilities are associated with $N_1 + N_2 - 2 = 36$ degrees of freedom: $p = 0.05$, $t = 2.03$; $p = 0.01$, $t = 2.72$; $p = 0.001$, $t = 3.59$.

degree of lipemia in the 2.5, 4.0, and 5.5 hour samples, the peak being at the fourth hour. The association between degree of lipemia and shortening of clotting time was low, and the peak times for the 2 variables did not coincide. The coefficient of correlation between optical density and whole blood coagulation time shortening was computed, combining the observations for the periods 2.5, 4.0, and 5.5 hours. The result was an insignificant value, $r = 0.206$. Finally, as would be expected, there was no significant lipemia following the low-fat meal.

DISCUSSION

While this work was in progress, several events more firmly established our conclusion that a fat meal definitely tends to make the blood more coagulable in the next few hours. In the first place, we analyzed statistically the raw data from which Tulloch, Overman, and Wright[5] had concluded there was no effect. The

TABLE 3.—*Summary of the Statistical Analysis of the Data of Tulloch, Overman, and Wright[5] on 10 Subjects*

Time after meal, hours	0.5	1.0	2.0	3.0	4.0
Δ = mean shortening, minutes	2.4	3.1	4.6	4.3	2.6
Δ/S.E.$_\Delta$	1.81	4.12	3.80	3.15	2.31

For 9 degrees of freedom, t values are: $p_{0.05} = 2.26$, $p_{0.01} = 3.25$, $p_{0.001} = 4.78$.

Blood was drawn with previously unused syringes for each sample before and at 0.5, 1, 2, 3, and 4 hours after a fat meal and whole blood coagulation time was measured. "Shortening" here is the difference between the control and the post-meal value.

statistical analysis, summarized here in table 3 demonstrates clearly that these "negative" results actually show a statistically highly significant shortening of the coagulation time, especially at 1.0, 2.0, and 3.0 hours after the meal. The error in the previous conclusion resulted from arbitrarily assuming a value for method uncertainty and failing to make any statistical analysis. However, we have no explanation for the only other negative finding, that of Manning and Walford.[9]

More important was the discovery of the work of Salvini and Sordi,[11] of Vandenbroucke and co-workers,[12] and the publication of the paper of O'Brien.[13] Salvini and Sordi drew blood from 10 men before and at 2, 4, and 6 hours after eating 100 Gm. of butter and measured the coagulation time of recalcified plasma, using the method of Quick,[14] the prothrombin activity as estimated by Scardigli and Mininni,[15] the amount of heparinoid materials by the method of Gibson and associates,[16] and plasma turbidity. They found maximal turbidity at 4 hours, at which time there were a moderate shortening of clotting time and increase of prothrombin activity together with a marked fall in heparinoid substances. Vandenbroucke and associates[12] also found a significant shortening of clotting time after a fatty meal.

O'Brien[13] found that a fatty meal containing 50 Gm. of animal fat had no effect on clotting of whole blood in the presence of platelets and a wettable surface, but in siliconized tubes there was a significant shortening of clotting time that was not definitely related to the degree of lipemia. The chylomicron layer obtained by high speed centrifugation, however, was found to have some shortening effect on the clotting time, in conformity with some of the findings of Poole[2] in rats. Very recently, Robinson and Poole[3] offered evidence suggesting that the active materials in chylomicra do not include triglycerides, cholesterol, lecithin, or phosphatides of serine or inositol, but that ethanolamine phosphatides may be suspect.

SUMMARY

Measurements of whole blood coagulation time in siliconized tubes, of prothrombin activity, of heparin tolerance, and of serum lipemia (turbidity) were made on blood samples drawn from 20 men at intervals of 1, 2.5, 4, and 5.5 hours after a meal of 300 ml. of 40 per cent butterfat cream and after a meal similar in calories but very low in fats. Parallel control measurements were made during continued fasting during the same period.

The whole blood coagulation time was significantly shortened after the fatty meal, especially at 2.5 to 5.5 hours, but was essentially unaltered after a nonfatty meal or during continued fasting. There was a trend toward shortening of prothrombin time after the fatty meal but this was of less significance because a similar, though less pronounced trend occurred after a nonfatty meal and during continued fasting. The heparin tolerance results indicated some relative prolongation of the heparin effect after both types of meal, particularly after the nonfatty meal, as compared with continued fasting. The degree of shortening of the clotting time after a fatty meal was not correlated to an important extent with the degree of lipemia (turbidity).

ACKNOWLEDGMENT

We are grateful to Dr. W. F. Sheeley, Director of the Hastings State Hospital, for making subjects and facilities available, and to Dr. J. T. Anderson, for help with the experiments.

SUMMARIO IN INTERLINGUA

Esseva executate mesurationes del tempore de coagulation de sanguine integre in tubos revestite de silicium, del activitate prothrombinic, del toleration de heparina, e del lipemia seral (turbiditate) in specimens de sanguine obtenite ab 20 homines a intervallos de 1, 2,5, 4, e 5,5 horas post un repasto de 300 ml de crema a 40 pro cento de grassia de butyro e post un repasto de simile valores caloric sed a bassissime contento de grassia. Parallel mesurationes de controlo esseva facite durante le mesme periodo in statos de jejuno continue.

Le tempore del coagulation de sanguine integre esseva significativemente accurtate post le repasto grasse, specialmente a intervallos de 2,5 a 5,5 horas, sed illo esseva in principio inalterate post repastos non-grasse e durante le jejuno. Esseva notate un tendentia verso le reduction del tempore prothrombinic post le repasto grasse, sed isto esseva minus significative proque un simile (ben que minus pronunciate) tendentia occurreva post le repastos non-grasse e durante le stato jejun. Le resultatos del tests del toleration de heparina indicava un certe prolongation relative del effecto de heparina post ambe typos de repasto, specialmente post le repasto non-grasse, in comparation con le jejuno continue. Le grado del reduction del tempore de coagulation post repastos grasse non esseva correlationate a grados importante con le grado del lipemia (turbiditate).

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Morphologic Aspects of the Negativity of the U Wave and their Corresponding Electrocardiographic and Clinical Data

By D. Furbetta, M.D., F. Santucci, M.D., A. Bufalari, M.D., and P. Solinas, M.D.

The negative U wave has been studied in 200 electrocardiograms. Six different types of negativity of the U wave are recognized; a seventh type includes the alterations of the T-U segment. Electrocardiographic and clinical data are correlated with these changes. Two hypotheses to explain the varying morphology of the negative U wave are discussed.

UNTIL quite recently neither the genesis of the U wave nor its diagnostic significance has been carefully studied. The description of the U wave generally has been limited to a statement that it is positive (upright), negative (inverted), or diphasic. Only negative deflections have been considered of some clinical diagnostic importance.[1-6]

In a previous paper,[7] we thoroughly examined the morphology of the upright U wave. Additional experience justifies the statement that a positive U wave is of much less significance than the more complex negative U wave, the clinical and morphologic aspects of which are discussed in this paper.

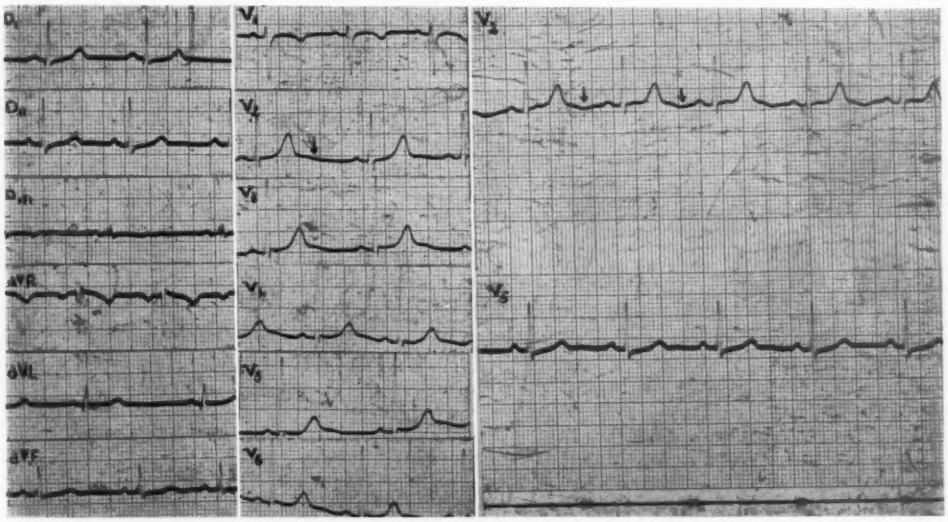

Fig. 1. In the right tracing, because of the careless placing of the exploring electrode, a downward deflection appears in lead V_2 that simulates a negative U wave. The left tracing from the same patient does not show inverted U waves in any lead.

Material and Methods

From our collection of 200 tracings with inverted U waves, 100 tracings were studied, both in the limb

From the Cardiological Center of the Institute of Clinical Medicine (directed by Prof. G. Dominici), Perugia University Medical School, Perugia, Italy.

and chest leads, or only in the latter. Only technically perfect tracings were included in order to eliminate artifacts that can lead to false interpretations. This selection is of importance, since negative U waves can be produced artificially. This has occurred once in our experience because of careless placing of the exploring chest electrode (fig. 1). We have found it useful and sometimes necessary to record 2 leads simultaneously because adequate evaluation requires comparison of findings in other more selective leads of the same electrocardiogram. The best paper speed to record clear waves seemed to be 40 mm./sec.

Observations

The morphology of the inverted U wave has been studied in comparison with the amplitude, duration, and location of the upright U wave elsewhere in the same electrocardiogram. The positive U wave will be referred to as the "basal" U wave. In the limb leads neither positive nor negative U waves change their fundamental morphology. Therefore, in 2 synchronously recorded limb leads, the points of maximal height and maximal depth of the positive and negative U waves occur simultaneously.

The inverted U wave has been most frequently described as a small deflection with

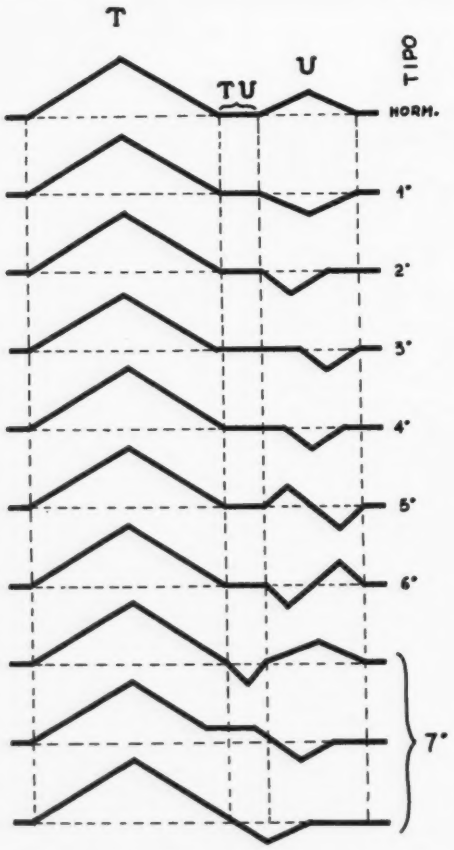

Fig. 2. The drawings illustrate the 6 morphologic types of negative U wave and a seventh one dealing with alterations of the T-U segment.

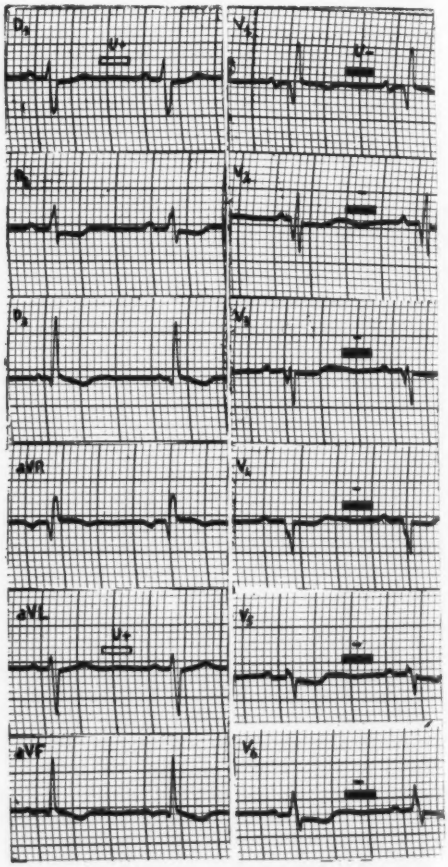

Fig. 3. Patient with tight mitral stenosis and tricuspid incompetence, right ventricular hypertrophy and strain. Negative U waves of the first type in every chest lead. U-wave duration was measured in lead I and aV_L.

the descending limb shorter than the ascending limb. Our studies have shown that in the chest leads morphologic aspects of the inverted U wave are much more complex. We have schematically classified these variations into 7 patterns, which are described in figure 2.

We have also included in our study of the negative U wave the variations of the T-U tract (end of the T, beginning of the U) because of their close morphologic relationship and clinical and electrobiologic significance, suggesting the possibility of a unitary genesis. The 7 types are characterized as follows.

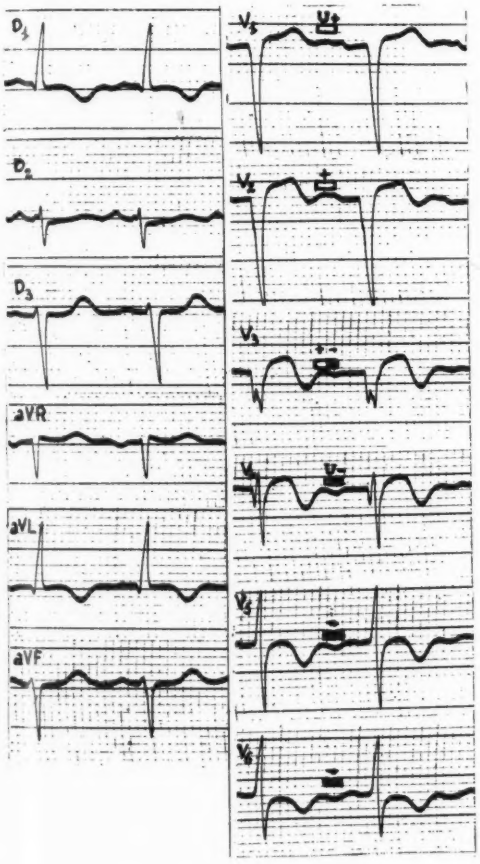

FIG. 4. Anteroseptal myocardial infarction between second and third stage. Negative U wave of the fifth type in V_3 and of the first type in V_4, V_5, and V_6. U-wave duration was measured in V_1.

1. The U wave is negative with varying amplitude. Compared with the "basal" positive U in another chest lead of the same electrocardiogram, its length does not show any variation. This type is characterized by a total inversion of the U wave (figs. 2–4).

2. The U wave is negative, but the inversion is present for only the initial one half or two thirds of its entire duration, as determined in the "basal" U wave of the same electrocardiogram. The final part of the wave is isoelectric (figs. 2, 5–7).

3. In this type the inversion is seen in the terminal one half or two thirds of the U wave, while the initial portion appears isoelectric (figs. 2 and 8).

4. The negativity occupies the central part of the wave, while the initial and final parts are isoelectric (figs. 2 and 9).

5. The U wave is diphasic "plus-minus" (figs. 2, 4, and 10).

6. The U wave is diphasic, but "minus-plus" (figs. 2, 5–7). In this type, as in the previous one, it is often possible to observe an equal development of the 2 components "minus" and "plus" of the diphasic wave.

7. This type includes the various morphologic anomalies of the T-U segment. It is most often depressed, but it may be elevated or sloped downward or upward (figs. 2, 7, and 11).

The modifications of the T-U segment are usually associated with anomalies of the U wave itself. More often elevation of the T-U is followed by the first, second, or sixth type of inverted U wave (fig. 7), while depression of the T-U is followed by an upright U, which becomes inverted subsequently.

Frequently different types of inverted waves are seen together. Usually a diphasic U wave of the sixth type in the right chest leads is associated with a negative wave of the second type in the left chest leads (figs. 4–7).

The incidence of the various types, the chest leads in which they appear, and the correlated electrocardiographic and clinical data are presented in table 1.

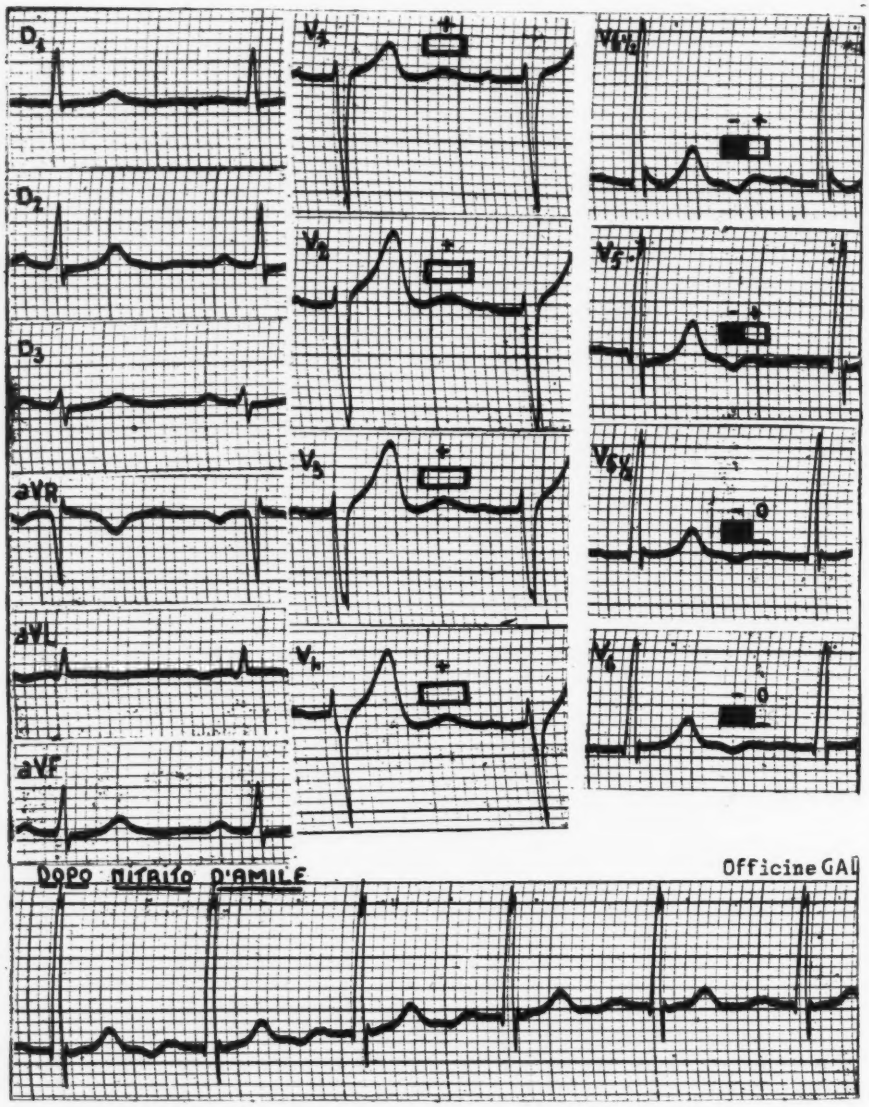

FIG. 5. Patient with mitral and aortic heart disease and left ventricular hypertrophy. Negative U wave of the second type in leads $V_{5\frac{1}{2}}$, V_6, and of the sixth type in $V_{4\frac{1}{2}}$, and V_5. Symmetric upright U wave in V_3, V_4. U-wave duration was determined in V_2. Note the disappearance of the inverted U wave after administration of amyl nitrite.

DISCUSSION

Our investigation of the possible patterns of the inverted U wave and their electrocardiographic and clinical correlations permit conclusions that are of interest though their significance remains obscure.

In a small percentage of cases the negative U wave had the same characteristics as the corresponding positive one. In 66 per cent of

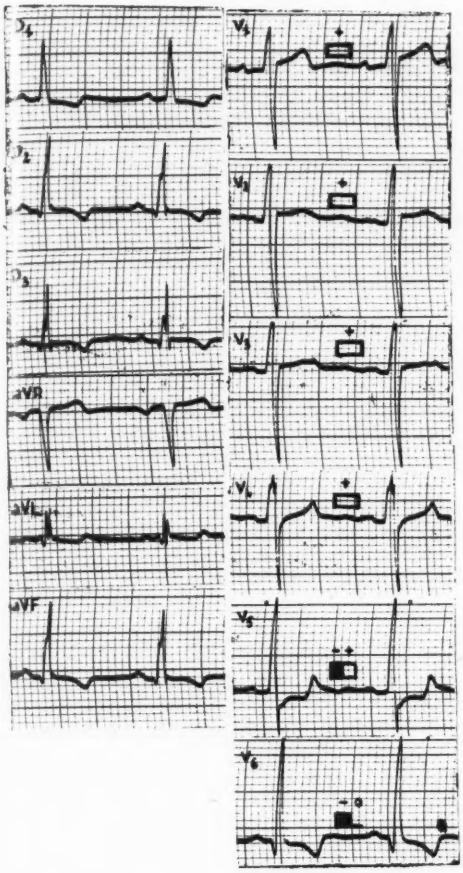

FIG. 6. Patient with mitral and aortic heart disease, left ventricular hypertrophy and strain. Negative U wave of the sixth type in V_5 and of the second type in V_6. U-wave duration was measured in V_2.

our electrocardiograms, the inverted U wave was of shorter duration than an upright U wave in other leads of the same electrocardiogram. In 21 per cent of the tracings it was diphasic with prevalence of the "minus-plus" type.

The most common types of precordial negative U wave were the second (negativity of the proximal portion) and the sixth ("minus-plus" diphasism). They were usually seen in patients with arterial hypertension and aortic valvular disease and in electrocardiograms showing left ventricular hypertrophy and strain. The second and sixth types were also found in electrocardiograms with signs of coronary insufficiency.

In myocardial infarction inverted U waves of the second type were usually found in association with patterns of the third stage or with residuals of old infarcts. In recent infarctions inverted U waves of the first type (negativity of the whole wave) or third type (negativity of the final portion) were more common.

In electrocardiograms with right ventricular hypertrophy due to mitral stenosis, inverted U waves were found only in the right chest leads, and their negativity was mainly of the first type (total wave inversion) or fourth type (negativity of the central portion).

The observation that precordial negative U waves in diseases affecting the right side of the heart differ, not only in their location, but also in their particular configuration, from those in left-sided heart disease might suggest that the left ventricle is responsible for the genesis of the initial portion of the U wave, while the terminal part depends on the right ventricle. Therefore, in left-sided heart disease, the negativity of the U wave in most of the cases occupied only the initial part of the wave. However, this hypothesis is not accepted by us.

Theoretically another possibility, which we endorse, is that the U wave is the summation of partial U waves, with origins from the right and the left ventricle. Hence in different pathologic conditions, 1 of the 2 components predominates, so that it causes a particular behavior of the resulting spatial vector and, consequently, in extreme cases, the negativity that we have described. According to this hypothesis, the various types of negative U waves do not depend for their origin on one or the other ventricle. They depend on the particular aspects of the spatial vector of U, resulting from the partial spatial vector of the unaffected ventricle and the preponderant spatial vector of the ventricle subjected to strain.

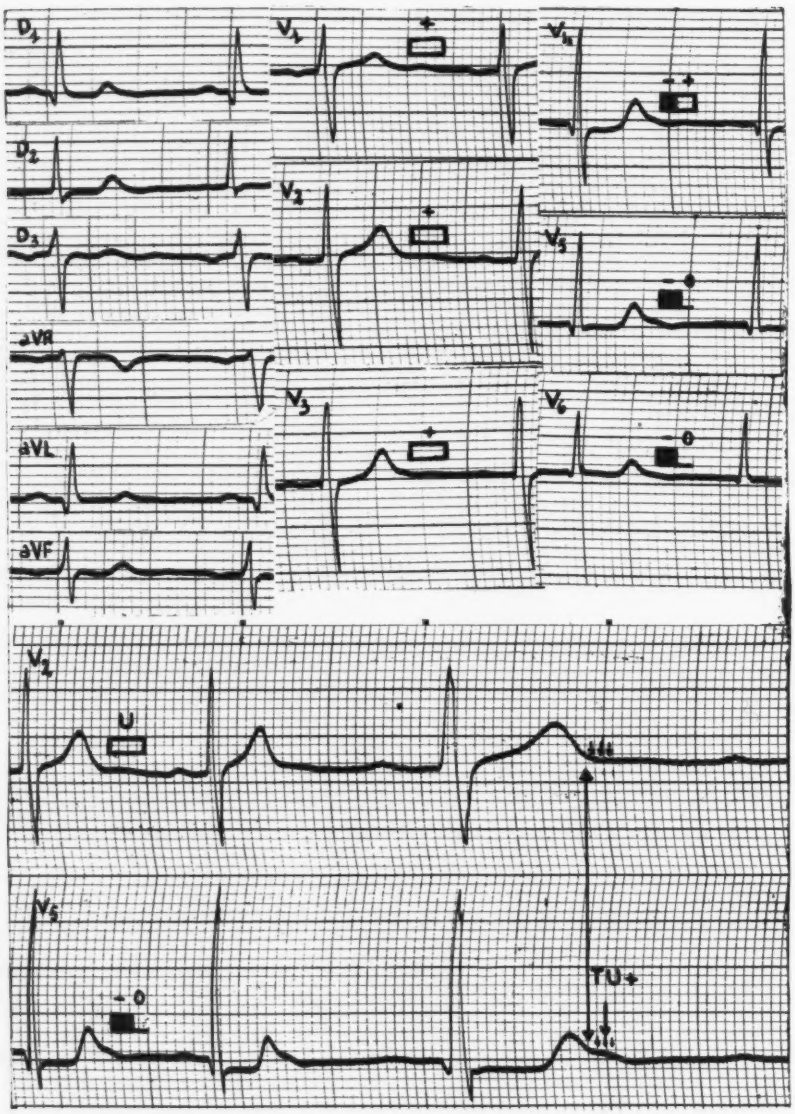

FIG. 7. Patient with mitral heart disease. T-U segment elevation combined with negative U wave of the sixth type in V_4 and of the second type in V_5 and V_6. U-wave duration was measured in V_1.

Finally, only the direction of the resultant spatial vector has electrobiologic and clinical significance; the various morphologic aspects of the negative U wave mean an abnormal and more obscure behavior of the instantaneous vectors in the development of the vector loop.

The T-U segment was present in most of the cases of inverted U wave and very often showed some deformities. Frequently it was elevated above the base line and followed by the negative U wave; it rarely appeared depressed without changes of the U wave.

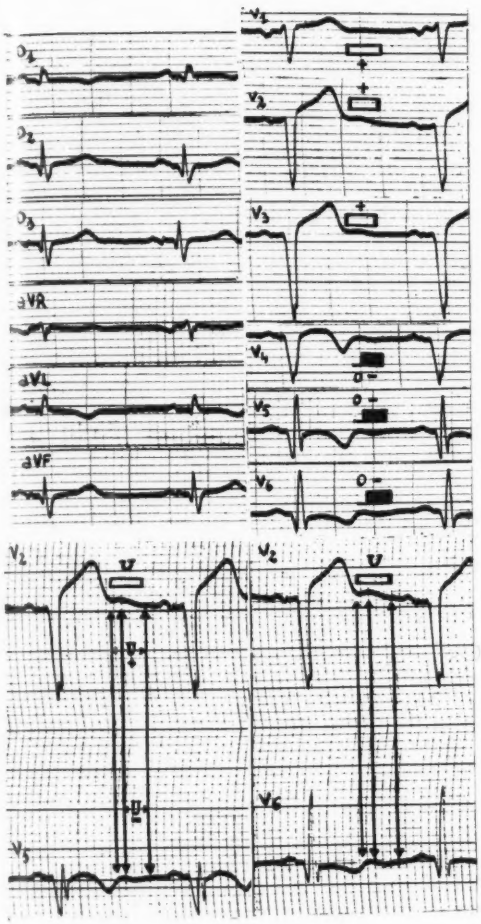

FIG. 8. Anterolateral myocardial infarction (third stage). Negative U wave of the third type in V_4, V_5, and V_6. U-wave duration was measured in V_2.

It seems possible, therefore, that alterations in the T-U segment originate from the same electrobiologic factors that produce abnormalities of the S-T segment.

SUMMARY

A careful examination of the morphology of the negative U wave led to the recognition of 7 different types. Modifications of the T-U segment were evaluated as equivalent to an inverted U wave.

After a correlation of the electrocardiographic and clinical data with the various types of negative U wave, 2 hypotheses were considered as explanations of the varying morphology. It is believed that the various

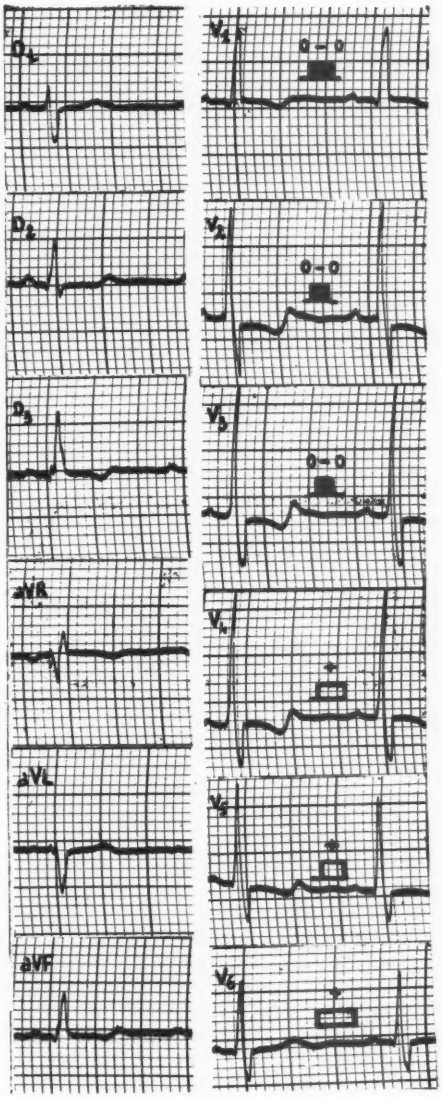

FIG. 9. Patient with pure mitral stenosis, right ventricular hypertrophy and strain. Negative U wave of the fourth type in V_1, V_2, and V_3. U-wave duration was measured in V_6.

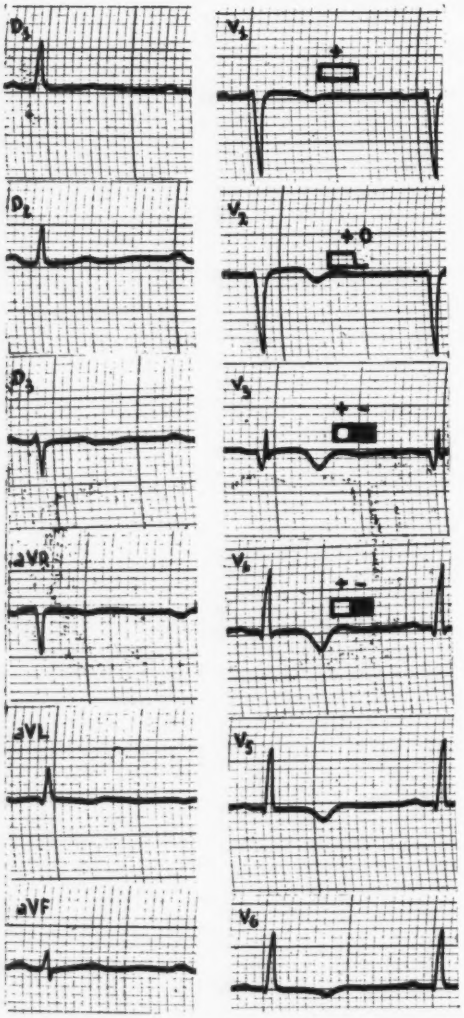

FIG. 10. Anteroseptal myocardial infarction (third stage). Negative U wave of the fifth type in V_3 and V_4. U-wave duration was measured in V_1.

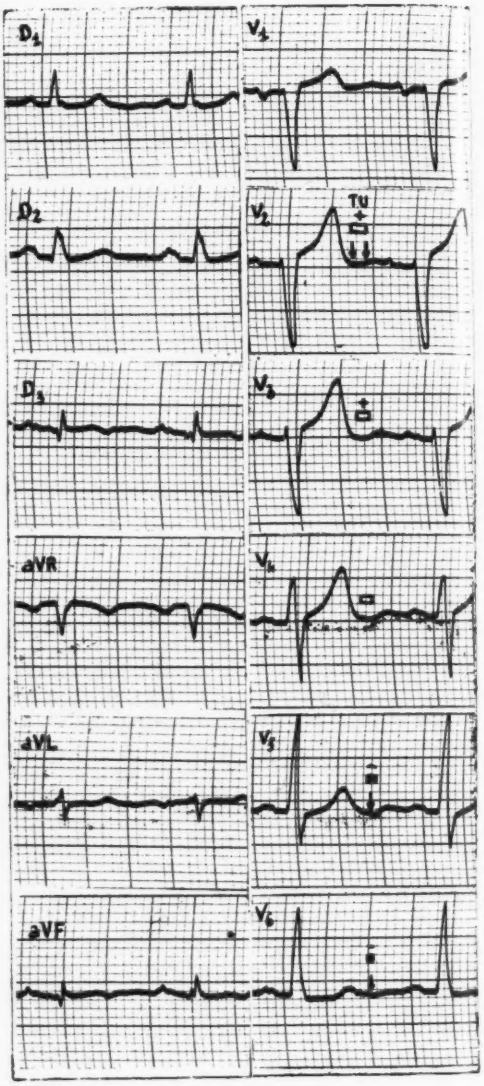

FIG. 11. Patient with hypertensive heart disease and angina pectoris and left ventricular hypertrophy. Depressed T-U segment seventh type in V_5 and V_6. T-U was determined in V_2.

types of negative U waves represent the resultant spatial vector of the unaffected ventricle and the preponderant spatial vector of the ventricle subjected to strain.

SUMMARIO IN INTERLINGUA

Un caute examine del morphologia del negative unda U resultava in le differentiation de 7 typos. Modificationes del segmento T-U esseva evalutate como equivalente de un invertite unda U.

Post correlation del datos electrocardiographic e clinic con le varie typos de negative

TABLE 1.—*Distribution of Abnormal Morphologic Types among 100 Cases of Negative U Waves and T-U Segments in Precordial Leads*

Type / Characteristics	I −	II −0	III 0−	IV 0−0	V +−	VI −+	VII −TU	Total
Electrocardiographic Pattern								
Right ventricular hypertrophy (V_1–V_3)	3			1				4
Right bundle-branch block (V_1–V_4)		1						1
Left ventricular hypertrophy (V_4–V_6)	3	9		1		11	1	25
Left ventricular hypertrophy and "strain" (V_4–V_6)		26				2	1	29
Left bundle-branch block (V_3–V_6)		3				1		4
Coronary insufficiency (V_3–V_6)		5		1	1	1		8
Recent infarction (V_3–V_6)	5		1					6
Old infarction (V_3–V_6)		7	4					11
Isolated U-wave inversion (V_4–V_6)		7			1	4		12
Clinical Data								
Arterial hypertension	3	20				9		32
Arterial hypertension + angina pectoris		14		1		5	2	22
Arterial hypertension + old infarction		5	1					6
Arterial hypertension + aortic heart disease		4						4
Angina pectoris		8	1		1	2		12
Myocardial infarction	5	2	4		1			12
Mitral heart disease (mitral stenosis and insufficiency)		3				2		5
Mitral stenosis	3			1				4
Aortic heart disease		2				1		3
Incidence	11%	58%	6%	2%	2%	19%	2%	100%

* Each electrocardiographic pattern is followed by the leads in which the negative U waves or T-U segments occurred.

undas U, duo hypotheses esseva considerate como explicationes del variationes morphologic. Nos opina que le varie typos de negative undas U representa le resultante vector spatial del non-afficite ventriculo e le preponderante vector spatial del ventriculo subjicite al stress.

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CLINICAL PROGRESS

Clinical Evaluation of Antihypertensive Drugs

By IRVINE H. PAGE, M.D., AND A. C. CORCORAN, M.D.

THE evaluation of antihypertensive drugs has become a big business. Hundreds of people who work in some aspect of clinical investigation spend at least part of their time in this process. Their observations determine the expenditure, first by the drug companies and then by the public, of some millions of dollars a year. Even the law recognizes the fact that no accumulation of pharmacology, however sound, and no amount of promotion can do anything for a drug which has not had a reasonably adequate clinical trial. Everyone acknowledges that it is the crucial aspect determining drug sale. But so far no one has paid much attention to the definition of the term, "adequate" or the characterization of the proper means of study of an antihypertensive drug.

This is partly because it is a new field of effort. Less than 10 years ago we used to plead with manufacturers to turn their attention to the field of antihypertensive medication. But, in a world in which the industrial emphasis was on antibacterials and vitamins, and with the medical profession apparently satisfied with garlic and phenobarbital, we got very little response. At long last, the commercial possibilities of a chronic and very common disease have been abundantly recognized and the dam has broken. The ensuing flood of drugs has taken most investigators by surprise, finding them without real agreement on technics and procedures. As a result, there is a great deal of repetition and of waste effort, and the investigator too often deserts his legitimate field of basic scientific study to spend his time in a process in which he may eventually become enmeshed.

The definition of what is a proper study of an antihypertensive drug or procedure is by no means easy. Those of us who attempt this process look with real envy on our colleagues who deal with the clinical trial of antibacterial drugs. They are concerned, for the most part, with diseases of brief duration and well-defined course and, above all, with such unexceptionable measurements as those of fever and leukocytosis. We, on the other hand, deal with a process usually of long and, very often, of unpredictable duration and with, as one of our basic measurements, arterial pressure, a notoriously labile function. The field is, therefore, very naturally vexed and confused. Claims and counterclaims are continually made. There is even some competition among investigators for the latest drug, some natural tendency to puff it at a scientific meeting. As a result, the literature abounds with unimaginative research and shows occasional lapses into flagrant lauding of the latest product at hand.

Our own studies in the treatment of hypertension have nearly always been concerned with patients who have severe or "malignant" hypertensive disease. There are two reasons for this choice. One is that the procedures we have had available, first anterior nerve-root section, then lumbodorsal sympathectomy and, later, kidney extracts and pyrogens, were admittedly somewhat heroic. Like the Mikado, we wished to let the punishment fit the crime. Next, the problem extends beyond the blood pressure; people die, not of hypertension, but of hypertensive disease. In this selected group of patients we had to deal with hypertensive disease as well as with hypertension, with a

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serious indication for treatment, with a reasonably certain prognosis, and with consistently and severely increased blood pressure.

Most such patients are glad enough to enter the hospital, so that this selection has directed us to technics of clinical trial in hospital. We believe that this has been a fortunate, if involuntary, choice; we have no intention of decrying the efforts of those whom circumstances force into clinical study of milder hypertensive disease in offices or out-patient departments. In fact we do this ourselves, since we quite agree that the value of a drug can only be assessed finally in terms of its activity under the normal circumstances of daily life. On the other hand, the concentration on severe hypertensive disease in the hospital has the real advantage of a potentially well-controlled experiment, and one that can yield reasonably accurate information from a small number of patients.

What Blood Pressure?

If we dismiss as premature the speculations that some of the available antihypertensive drugs, with the specific exception of sympatholytic agents in pheochromocytoma, have definable points of attack on the basic mechanisms responsible for hypertension, then the basic rationale of antihypertensive therapy depends on our recognition of the fact that severe and persistent high blood pressure is bad for the vessels. In this light, anything that is reasonably safe and tolerable and that produces by almost any means a persistent decrease of blood pressure is a potentially useful antihypertensive drug. Hence, much as we would like to deal only with the basic problem of hypertensive disease as such, we are forced to depend on measurements of blood pressure. The question is what pressure?

The measurement we would like to have is one that would be representative of the patient's blood pressure as it is most of the time. The basal blood pressure, which is rather tediously secured, probably does not meet this requirement. Certainly the casual "resting" blood pressure does not, even when it is indefinitely multiplied. Casual readings are usually high. A minority of patients show waking, presumably basal pressure readings, consistently higher than their casual, resting pressures as measured in the afternoon. Reliance on uncontrolled, casual readings accounts for most of the vexatious claims in this field.

We have arbitrarily resolved this difficulty by dealing with weekly averages of supine, resting pressures. And, with the advent of drugs that cause orthostatic drops in pressure, we have added averages of standing pressures. Others, using these drugs, have measured sitting pressures and, since most people with severe hypertension sit a good deal of the time, this is probably also a representative datum. Our usual procedure is to average the pressures weekly of the readings made twice daily. The average obliterates most of the peaks and the valleys and provides only a single datum for a week's effort. But our experience indicates that this is a valid and representative datum.

The Control Period

Most of the difficulty with the assessment of drugs depends on the wide variety of opinions on what is a "reasonable" control period. We have reported our own experience elsewhere.[1] Briefly we have found that, in patients with severe or malignant hypertensive disease, the average from the first week in hospital tends to be higher by 8/5 mm. Hg for malignant hypertension and 10/5 mm. Hg for severe essential hypertension than the average of the second week. The averages of the second and third weeks usually correspond closely, although a minority of patients, usually those with milder disease, continue to show some decrease in pressure averages over three or more weeks. These decreases represent adaptation to the ordered hospital routine, protection from the onslaughts of the world outside, the psychotherapeutic effects of close and sympathetic observation, and to these we often add the effects, if any, of placebo medication.

An extensive analysis[2] of the effects of prolonged hospitalization on means of basal blood pressures of patients with essential hypertension yields data similar to our own, in that the latter weeks of hospitalization usually demonstrate considerable stability of the means, while the mean of the first week's pressures and the

sequence of changes in pressure individually tends to be somewhat variable. Undoubtedly, there is no substitute for prolonged control observations. On the other hand, particularly in patients with demonstrably severe and advancing hypertensive disease, the means of the second and third weeks of pressures form representative indices of pressure level during hospitalization and, as such, adequate baselines for therapeutic study.

There is no doubt that this is a tedious and expensive process. But it has two large advantages. First, it provided us with a blood pressure datum that is truly significant. Secondly, time is made available for detailed clinical study and for the investigation of dubious points in the physical or laboratory examination. As a result, treatment begins only after the patient's status in terms of hypertensive disease is reasonably characterized.

The Estimate of Hypertensive Disease

This is made in terms of four panels, of which the diastolic blood pressure average is one. The others concern the cerebral and renal circulations and the heart. A large amount of data has accumulated to suggest that it might also be desirable to evaluate other data, such as serum β-globulin.

The estimate of cerebral vascular disease is either presumptive or objective; the presumptive evidence, still very unsatisfactory, is gathered from history of headaches, encephalopathy, mild seizures and, probably best of all, from a pooled estimate by several observers of the status of the fundi and retinal arterioles. The latter is made numerically in terms of constriction, sclerosis, exudate, hemorrhage, and papilledema, and this series of examinations is continued weekly.[1]

Fortunately, the renal panel, so important in these patients, is much more accessible than the cerebral. This circulation is assessed in terms of approximate filtration rate (from urea clearance) or plasma creatinine, often by measurements of plasma para-aminohippurate (PAH) and mannitol clearances for better definition, by measurements of maximum concentrating power (Addis test) and by quantitative determinations of urine protein and sediment.

Cardiac status is assessed in terms of functional capacity and, objectively, in terms of cardiac enlargement as determined by the teleroentgenogram and the electrocardiogram. When, as commonly happens, there is evidence of congestive heart failure, this is appropriately treated and brought to some optimum status before the control period ends.

The results of this study are plotted graphically in a "long chart" that has two large advantages: It permits rapid visualization of the trends of these significant functions during control and treatment periods and it is also a perpetual reminder to the investigator of examinations that may be inadvertently omitted. This chart (fig. 1), derived from one used by Dr. D. D. Van Slyke in his study of Bright's disease, has saved untold time in record-searching, and is freely and wholeheartedly recom-

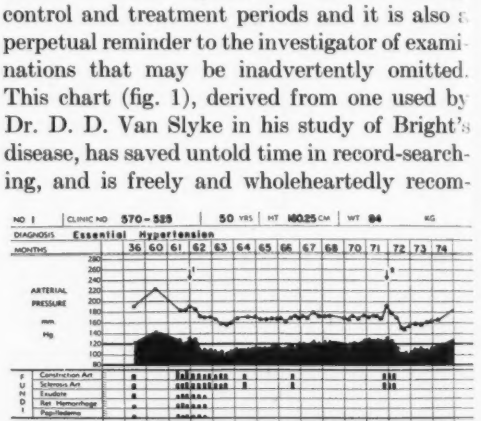
NO. 1
CLINIC NO. 570-525
50 YRS
HT 160.25 CM
WT 84 KG
DIAGNOSIS Essential Hypertension
MONTHS
36 60 61 62 63 64 65 66 67 68 70 71 72 73 74
ARTERIAL PRESSURE mm. Hg.
Constriction Art
Sclerosis Art
Exudate
Ret. Hemorrhage
Papilledema
FILTRATION RATE ml. per 1.73 m.² per min.
FILTRATION FRACTION
RENAL BLOOD FLOW ml. per 1.73 m.² per min.
URINARY CONCENTRATING POWER (Addis)
HEMATURIA erythros per 12 hrs.
PROTEINURIA Gm. per 24 hrs.
BLOOD HEMOGLOBIN Gm. per 100 ml.
PLASMA PROTEIN Gm. per 100 ml.
TRANS CARDIAC diameter % normal
E.C.G.

FIG. 1. A "long chart" showing how the data are graphically ordered. The chart is used along with the clinical notes as a continuous record of the course of the patient's illness.

ended as a tool in any prolonged therapeutic ial.

The results of this study can also be lumped gether into a single numerical "severity index,"[3, 4] in which a maximum score of 4 is signed to each of the four panels.

A maximum of four points each is assigned estimates of average supine diastolic pressure and of the extent of hypertensive vascular disease in the heart, kidneys and brain. For example, a patient with diastolic pressure averaging more than 140 mm. Hg, grade IV, heart failure, uremia and grade IV retinopathy, plus encephalopathy, would be graded 16; improvement in any category reduces the grade below 16.

Comparisons of pre- and post-treatment severity index in patients with like pretreatment indices is a useful way of summarizing the experience with a drug. We are well aware that the index we suggest is highly subjective in its scoring and that a vast amount of study might well be devoted to the compilation of one more objectively based on the solid datum of mortality in untreated patients. Such patients are now rare. Still, if there could be some agreement on this, or a like system of scoring, there would be less controversy about the value of this or that experimental drug or procedure in any large group of patients. The history of sympathectomy is a case in point and Dr. Smithwick's scoring is an attempt like ours, at securing comparability in the data.

Placebos and Blind Tests

We noted above that placebos are commonly given during the second and third weeks of the "control" period. Theoretically, there might be an advantage in starting the test period as a blind or double-blind experiment. But this procedure has serious disadvantages and is, in fact, impractical. We deal with highly vasoactive drugs. Quite apart from their effects on blood pressure, which most patients soon learn in one way or another, these all have side-effects that are definite and unmistakable. As a result, a blind test loses its point because the patient and the doctor very quickly recognize when a placebo is substituted for an active drug. We still attempt such substitution whenever it seems practical, which is usually when the dosage of active drug has been reduced to a point at which side-effects are not easily discerned. As a routine procedure, however, we doubt its value, and use the placebo during the pretreatment period.

It may seem heresy in some eyes that we believe it advantageous for the investigator to be specifically interested in, and enthusiastic about, the drug he is studying, and that there is a real scientific disadvantage in a dispassionate attitude. Two examples come to mind. One concerns hexamethonium, which was used and studied by Dr. F. H. Smirk with real devotion. As a result, his scrutiny was closer and his therapeutic results were better than ours or those of most other workers. His estimate of the status of this agent was more accurate than the appraisals of those who desultorily gave it to a few people and, troubled by side-effects, more or less sneeringly gave it up. The other concerns hydralazine; this has been widely despaired of as a useful medication; on the other hand, because our colleague, Dr. Robert Taylor, and we were fascinated by its properties, we used it in such a way that we have come to regard it as a very useful and often a lifesaving drug. This experience depended largely on our having enough enthusiasm for it to persuade ourselves and our patients that it was to their advantage to accept and control its common, initial, disagreeable side-effects.

The Out-Patient Study: Home Pressures

When the time comes for discharge from the hospital, there is no need to give up the experiment. As long as we relied on out-patient casual pressures we had few data from our out-patients that we would regard as convincing. Partly, this is because of the "break-through" of pressures under the emotional stimulus of a critical examination. Patients whose pressure averages at home or in the hospital were reasonably normal, frequently showed high casual resting pressures as out-patients. In fact, some of the best responders to hydralazine would not have been recognized as such had only the casual pressures been available (fig. 2). Rather, they would have been categorized as showing improvement in their hypertensive disease

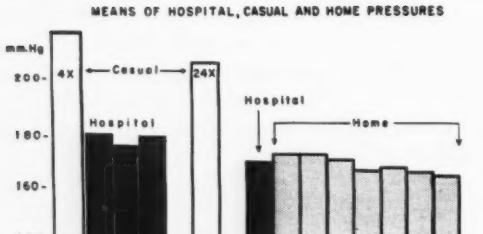

FIG. 2. Open bars are means respectively of 4 and 24 casual measurements of pressure; solid bars are weekly means of hospital pressures and cross-hatched bars are weekly means of home pressures. Hydralazine treatment was started on discharge from hospital and showed no effect as judged from casual pressures. Readmission to hospital established, by comparison of hospital means, that pressure had actually decreased, and this was confirmed by the subsequent means of home pressures. (Reproduced, with permission, from the Annals of Internal Medicine.[1])

without corresponding changes in pressure, as in the past, were so many sympathectomized patients. From such data as these, the erroneous conclusion has been drawn that, with this or that agent or procedure, hypertension and hypertensive disease are dissociated phenomena. As far as we know this is a very rare occurrence.

With the advent of the ganglion blocking agents, we embarked on a much wider program of home-pressure readings than before. Data have since accumulated to show that, in most patients, the home-pressure averages correspond fairly well to hospital averages and that a lack of such correspondence usually has a clearly definable connotation that bears on the patient's problem. We have also become impressed with the value of the datum provided by most of these patients as a basis for therapeutic trial and, in many of them, with the personal therapeutic advantage of knowing their blood pressure and knowing that it is under control. We would not recommend this procedure to everyone. Those who use it are a selected group. Only one out of some hundreds has demonstrated what might be interpreted as significant psychologic stress from the procedure; this was a young man who manifested the same psychologic stress to any procedure related to his hypertensive disease, which he was quite unwilling to accept.

The Cocktails

Each of the presently available, antipressor drugs has a limited field of usefulness. Some patients respond to one, some to another and not to the first. The dosage at which a response is obtained varies from person to person and, in the same person, from time to time. As a result, each drug has to be individually adjusted or, to adhere to the current jargon, "titrated." Many drugs, notably the sympatholytic and ganglion-blocking agents, elicit a state of tolerance more or less rapidly. This is perhaps a good thing. We have a sardonic suspicion that there would be a vast new field of significant illnes if most of the ganglion-blocking agents, in the dosages administered, were not almost inert in most of the people who take them.

These considerations weigh heavily against the dispensing of mixtures of hypotensive drugs. They do not bear on the possibility that some patients may gain an advantage from combinations of such agents. Of course they may. But they gain only when the dosage of each can be appropriately selected, which is not the case when these agents are all packaged together in one pill. The use of these mixtures seems to us scientifically and professionally indefensible unless it can be shown that there does exist some very unusual patient who has no problems of tolerance or specific responsiveness.

The Cost

Hospitalization is costly; the investigator's time and energy are costly; technicians are costly; thus, the whole process of clinical trial is enormously expensive. Probably the greatest expense is the time spent away from fundamental investigation and contemplation of

basic mechanisms, with all its attendant risks of ultimate intellectual sterilization of a potentially productive person. Very little of this cost is defrayed by those who receive the largest financial advantage. Perhaps this is as it should be. It may be that the psychologic boost of being "first" and of reading a paper each year on the merits of some new drug is reward enough. To our minds, this is not enough. Certainly there are many who would look with a jaundiced eye on a clinical trial that was wholly and effectively supported by the interested drug company. But the same critics would not hesitate to accept a report from the same investigator on an animal or chemical study, wholly subsidized and of potential commercial value. There must be some middle way between the present system, which inequitably distributes a large commercial cost on investigators, hospitals and patients, and an equitable method, which would not be open to the suspicion of commercial prejudice. The solution of this problem might well be a specific aspect of the function of the newly created Committee on the Investigation of Antihypertensive Agents, recently formed by the American Medical Association's Council on Pharmacy.

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Disease in man is never exactly the same as disease in an experimental animal, for in man the disease at once affects and is affected by what we call the emotional life. The physician who attempts to take care of a patient while he neglects this factor is as unscientific as the investigator who neglects to control all the conditions that may affect his experiment. The good physician knows his patients through and through, and his knowledge is bought dearly. Time, sympathy, and understanding must be lavishly dispensed, but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.—Francis Weld Peabody. *The Care of the Patient.* Harvard University Press, 1927.

CLINICAL CONFERENCE

EDITOR: EDGAR V. ALLEN, M.D.

Associate Editor: RAYMOND D. PRUITT, M.D.

Nonspecific Pericarditis and Myocardial Infarction

Their Differential Diagnosis

By JOHNSON MCGUIRE, M.D., ROBERT A. HELM, M.D., ARNOLD IGLAUER, M.D., RALPH C SCOTT, M.D., J. HAROLD KOTTE, M.D., AND BENJAMIN FELSON, M.D.

DR. JOHNSON McGUIRE: Within the past few years we, as well as others, have encountered a number of instances in which nonspecific pericarditis has been erroneously diagnosed as myocardial infarction.

The case reports and discussion that follow in this clinical conference serve to illustrate certain of the problems encountered in this important differentiation.

CASE 1

A physician, aged 37, who had hitherto enjoyed excellent health, suddenly developed severe precordial pain that radiated to the left shoulder and along the inner aspect of his left arm to the fingers. Shortly after the onset of pain, the physician listened to his own chest with a stethoscope and heard a pericardial friction rub.

He was admitted to the hospital with the diagnosis of coronary thrombosis and myocardial infarction.

Physical examination showed an acutely ill man with severe chest pain. The blood pressure was 120/80 mm. Hg, pulse 68, and respiratory rate 24. Physical examination suggested slight cardiac enlargement. No murmurs or gallop rhythm were heard. There was a loud pericardial friction rub. The physical examination was otherwise normal.

An electrocardiogram showed elevation of the S-T segments in leads I and II, interpreted as anterior myocardial infarction complicated by pericarditis. Initial x-ray examination of the heart showed slight enlargement thought by the roentgenologist to be due to cardiac hypertrophy rather than pericardial effusion. The white blood count was 15,500 with 75 per cent polymorphonuclear cells; sedimentation rate 60/mm./hr. (Wintrobe technic).

Anticoagulant therapy was instituted with dicumarol. The course in the hospital was characterized by recurring episodes of severe chest pain modified somewhat by changes in position of the body and by intermittent fever.

Dr. McGuire: Because of the appearance of the friction rub at the onset of the chest pain, the marked modification of pain with change of position, and the character of the serial electrocardiograms, the diagnosis of myocardial infarction was changed to that of acute nonspecific pericarditis and the subsequent course made this diagnosis quite clearly the correct one. It is probable that many patients with nonspecific pericarditis have been incorrectly and permanently labeled as having had myocardial infarction. From the point of view of peace of mind of the patient as well as insurability, such a mistake is unfortunate. Also, anticoagulant therapy in acute benign pericarditis is contraindicated as in 1 case, reported by McCord and Taguchi,[1] acute fatal hemorrhagic tamponade was described.

Physician: How quickly following myocardial infarction or the onset of acute nonspecific pericarditis do pericardial friction rubs develop?

Dr. McGuire: A pericardial friction rub most

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commonly appears on the second or third day following the infarction and usually disappears in a day or 2. In the case under discussion, the audible pericardial friction rub heard immediately after the onset of pain made the diagnosis of myocardial infarction questionable. The friction rub associated with pericarditis often appears within a few hours of the onset of pain, although cases have been observed in which the rub appears considerably later.

Physician: Is variation in the intensity of the pain with change of position commonly present in patients with myocardial infarction with complicating pericarditis?

Dr. McGuire: In our experience, modification of chest pain with change of position in myocardial infarction, with or without pericarditis, is very rare. However, in patients with acute nonspecific pericarditis intensification or relief of pain with change of body position is common. Rotation of the trunk, change from recumbency to the sitting position, or deep breathing may profoundly alter the severity of the pain. Severe pain is rarely present in the pericarditis due to tuberculosis or rheumatic fever. A possible explanation, as suggested by Burchell,[2] is that a portion of the inner aspect of the parietal pericardium, like the epicardium, is insensitive to pain while the exterior surface of the parietal pericardium, like the pleura, when inflamed, causes severe pain.

Physician: Is the radiation of pain helpful in the differential diagnosis?

Dr. McGuire: The pain of both myocardial infarction and pericarditis may radiate to the left arm and hand, but the pain of pericarditis rarely extends to the right arm. Back, shoulder, and lower neck pain occur in both diseases. Pain in the jaw or teeth with pericarditis has been reported, to our knowledge, in only 1 case.[3]

Physician: Are antibiotics of value in the treatment of acute nonspecific pericarditis?

Dr. Arnold Iglauer: Despite a few case reports of apparent benefit from broad spectrum antibiotics and streptomycin, the improvement of these patients may well have been coincidental. In our experience, antibiotics have apparently been of no benefit. Steroid therapy in a few reported instances in which it has been used has produced symptomatic improvement.

Physician: In what way does x-ray examination help to differentiate pericarditis from myocardial infarction?

Dr. Benjamin Felson: Radiologically speaking, this distinction may be difficult or impossible to make, as in both conditions the chest film may appear entirely normal.

Unfortunately, most cases of myocardial infarction and benign pericarditis do not produce typical x-ray changes in heart configuration. However, even in these instances roentgen study may still prove helpful. Thus, localized pulmonary infiltrate is sometimes associated with benign pericarditis, whereas widespread pulmonary congestion and edema may occur from cardiac failure following myocardial infarction. The cardiopericardial silhouette may rapidly enlarge soon after the onset of either condition, but it occurs more frequently and to a greater degree in benign pericarditis. Whether dilatation of the heart or small effusion is responsible for the rapid fluctuations in size of the cardiac silhouette is still a controversial question. Fluoroscopically, recent infarction at or near the cardiac apex quite often results in a localized segment of impaired, absent, or even paradoxical pulsation, whereas impairment of pulsation resulting from benign pericarditis with effusion is more generalized and, if anything, more evident along the right border.

If benign pericarditis results in an extensive effusion, evidence of a large pear-shaped contour, rapid change in size of the cardiovascular silhouette, impaired pulsation, and the occurrence of noncongested lung fields all offer confirmation of the diagnosis. Contrary to the statements in many textbooks, changes in the contour of the pericardial silhouette with change from the upright to the Trendelenberg position has not proved of differential diagnostic value, since the flabby dilated heart also apparently enlarges at the base in the reclining position.

Physician: Does angiocardiography help in the differential diagnosis between dilatation and effusion?

Dr. Felson: Yes. When the dye-filled cham-

bers of the heart are seen well within the shadow of the cardiac silhouette, one can be certain that pericardial effusion is present rather than cardiac dilatation.

Dr. McGuire: The second case, which was initially incorrectly diagnosed as myocardial infarction, emphasizes additional features of differential diagnostic value.

Case 2

A. McC., a 55-year-old truck driver, who had had pleuritic left chest and left shoulder pain for 10 days, was admitted to the hospital because of an increase in the intensity of the pain accompanied by an episode of syncope. Positive physical findings included a temperature of 100.4 F., blood pressure of 90/64 mm. Hg, pulse of 72, with frequent premature contractions, pallor, profuse perspiration, slightly distended neck veins, distant heart sounds, and moist rales at the left lung base. The admission diagnosis was myocardial infarction. The blood pressure rose to 112/90 without specific therapy. A transient pericardial friction rub was heard on the fourth hospital day.

Laboratory findings included a polymorphonuclear leukocytosis of 17,500 and a sedimentation rate of 32 mm. per hour. Chest x-ray on the second hospital day showed the transverse diameter of the cardiac silhouette to be 16 cm.; of the chest, 28 cm. There was slight haziness in the left lower lung field and, in addition, a small left pleural effusion. On the twelfth hospital day the cardiopericardial shadow had diminished to 14.5 cm. and the lung fields were clear. Cardiac pulsations were normal on fluoroscopy.

Electrocardiograms 8 and 4 days before hospitalization showed only minimal S-T elevation in the standard leads and several precordial leads. During the first 4 days after admission there was slight S-T elevation in the standard leads with rather marked S-T elevation in V_2 and V_3 and progressive flattening and inversion of the T waves in the standard leads and in V_4, V_5, and V_6. An electrocardiogram on the fifteenth hospital day showed inverted or diphasic (+ −) T waves in leads I, II, aV_L, V_2–V_6. All tracings demonstrated frequent premature ventricular contractions.

Fever and pain gradually subsided. The patient was discharged after 3 weeks of hospitalization and has since remained well, having returned to his strenuous occupation. The discharge diagnosis was acute nonspecific pericarditis. An electrocardiogram approximately 2 months after the onset of the illness was within normal limits except for a flat T_1.

Dr. J. Harold Kotte: This case brings to mind 2 other features of acute pericarditis, namely the common association of pleural or pulmonary lesions and the relative infrequency of shocklike symptoms. Pneumonitis or pleurisy may precede the development of pericarditis, and pain from the latter may merge with that of pleuritis and obscure the diagnosis unless variation in the pain pattern is considered carefully.

Fall in blood pressure with attendant weakness, sweating, and impairment in level of consciousness may occur briefly at the onset of pericarditis but rarely reaches the magnitude observed in myocardial infarction. Manifestations resembling shock are probably due to vasodepressor reflexes originating from severe pain, as was apparent in this case from the development of fainting and absence of concomitant tachycardia. Rarely cardiac tamponade may be sufficiently severe to produce the manifestations of shock. There has been 1 report[4] of a probable case of nonspecific pericarditis with death from peripheral circulatory failure shortly after the onset of the illness. In the majority of patients with this condition, the manifestations of tamponade are not sufficiently marked to require pericardiocentesis.

Physician: What are the characteristic electrocardiographic findings in acute nonspecific pericarditis in contrast to the alterations that occur with myocardial infarction?

Dr. Robert A. Helm: In the acute stage of pericarditis the S-T segments are typically elevated in all 3 standard leads and in most or all of the precordial leads. Lead aV_R, as conventionally recorded, displays S-T depression. In myocardial infarction the S-T displacement frequently takes opposite directions in leads I and III, and the S-T segment elevation may be limited to a few precordial leads with isoelectric or depressed S-T segments in the remainder of these leads.

The elevated S-T segment in pericarditis usually takes a straight course or has a curvature that is concave upward. This has been emphasized as a distinguishing characteristic in contrast to the frequently upward convexity of the elevated S-T segment of myocardial infarction. In our experience, the S-T contour

in both conditions is sufficiently variable that this differential point has only limited diagnostic value. The S-T segment displacement in pericarditis may not be marked and is sometimes within the limits of what is considered to be normal. In such instances, observation of serial tracings for the evolutionary changes characteristic of pericarditis is most helpful. The S-T segments usually return to the baseline within or at the end of the first week. Although rarely the T waves remain upright, characteristically they flatten and begin to invert. The inversion is usually symmetrical. In this intermediate stage the flattened T waves may be notched. The T waves may remain inverted or flattened for weeks or months and frequently show variations in their depth and contour from day to day despite absence of other evidence of active disease. It has been stated that, in contrast to infarction, T-wave inversions do not occur in pericarditis until the S-T segments return to the isoelectric level. This is not a universal finding, however, and the cove-plane S-T and T contour classically associated with infarction may be seen in pericarditis.

Pericarditis does not distort the QRS complex except that pericardial effusion may diminish the voltage; slight positional variation of the QRS axis may also occur. Pathologic Q waves characteristic of infarction are never seen. However, the electrocardiographic diagnosis of pericarditis presents a problem when the S-T and T-wave changes that it produces must be differentiated from those caused by myocardial injury and ischemia or by infarction occurring without alteration of the QRS complex. Thus, Pruitt and his associates[5] found massive T-wave inversion in precordial leads (without QRS alteration) to be associated frequently with subendocardial infarction or with coronary insufficiency; such changes may be indistinguishable from those sometimes seen in the subacute or chronic stage of pericarditis. If, in such a circumstance, a friction rub is present, the diagnosis of pericarditis is much more likely. Myocardial infarction produces a friction rub only when it is transmural or when it involves at least the epicardium. In such instances the absence of significant alteration in the QRS complex, indicative of infarction, is probably rare in view of the experimental work carried out in Prinzmetal's laboratory.[6] Likewise, when acute myocardial infarction is complicated by pericarditis leading to electrocardiographic changes from the latter, QRS alteration resulting from the infarction is usually present.

Premature contractions may occur as in this second case but serious arrhythmias and various degrees of A-V block are exceedingly rare in nonspecific pericarditis and are much more common in myocardial infarction.

The effect of exercise on the electrocardiogram during pericarditis has received relatively little attention. S-T segment elevation, occurring as a normal variant, disappears with exercise; in acute pericarditis the segment shift is said to persist but a sufficient number of patients with this condition have not been subjected to exercise to indicate that this is a universal finding. Transient inversion or deepening of already inverted T waves have been reported to occur with the Master 2-step test in patients who were convalescing from pericarditis. We have observed such a "positive" exercise test in 2 such cases. On the other hand, patients who have recovered completely from pericarditis show no higher incidence of abnormalities after exercise than would be expected in the general population. Thus, Carmichael and his associates[3] observed no significant deviations from the resting record in patients who had had nonspecific pericarditis 2 or more years previously.

Physician: Would you discuss the electrophysiology of the electrocardiographic changes found in pericarditis?

Dr. Helm: There are 2 important pathologic characteristics of pericarditis that explain the electrocardiographic findings. Firstly, only the superficial epicardial layer of the myocardium is involved and, secondly, the process is usually diffuse rather than localized. The absence of involvement of a significant portion of the myocardium accounts for the absence of alteration of the contour of the QRS complex. This same pathologic characteristic explains a

finding that is emphasized in Lepeschkin's text[7] but that apparently has not received general attention. In a lead demonstrating an Rs complex, elevation of the S-T segment resulting from pericarditis will not obliterate the small s wave but will displace it above the baseline so that it forms a well-defined notch on the lowest portion of the descending limb of the R wave. This is well illustrated in a number of tracings of pericarditis published in the literature and has been seen in our own material. It may be explained by the hypothesis that in pericarditis the S-T segment elevation does not begin until the activation front has reached the epicardial surface. In myocardial infarction the S-T segment elevation commences earlier in the QRS complex, since the area of injury extends into the subendocardial region. A small s wave is therefore obliterated by the S-T segment elevation accompanying infarction. Perhaps differences in the contours of the S-T segments in the 2 conditions may be similarly explained by differences in the time of onset of the S-T segment shift with respect to the last portion of the QRS complex inscribed from areas of myocardium not involved by the pathologic process.

There are 2 explanations for the development of S-T segment shift in pericarditis:

1. A difference in potential develops between the inflamed, partially depolarized epicardium and the adjacent resting or polarized myocardium resulting in displacement of the T-P segment in either an upward or downward direction, depending on the direction of the lead axis as described below during the *diastolic* phase of the cardiac cycle. Although no longer isoelectric, the T-P segment continues to be taken as the baseline of the tracing, since its actual shift could not be apparent unless the injury were actually to occur during the inscription of the record. The S-T segment, which, according to this explanation, remains isoelectric, is then inscribed at a different level than that of the T-P "baseline."

2. The process of electric activation may fail to penetrate or may only partially penetrate the injured area. This results in a failure of the S-T segment to return to the isoelectric level during the *systolic* phase of the cardiac cycle, since a potential difference exists between the polarized or only partially depolarized epicardium and the adjacent, completely depolarized myocardium. According to this explanation, the T-P segment remains isoelectric.

Hellerstein and Katz[8] recorded continuous tracings during the experimental production of injury to various portions of the heart. They showed that both explanations are applicable in that systolic displacement of the S-T segment and diastolic displacement of the T-P segment occurred simultaneously, each to a

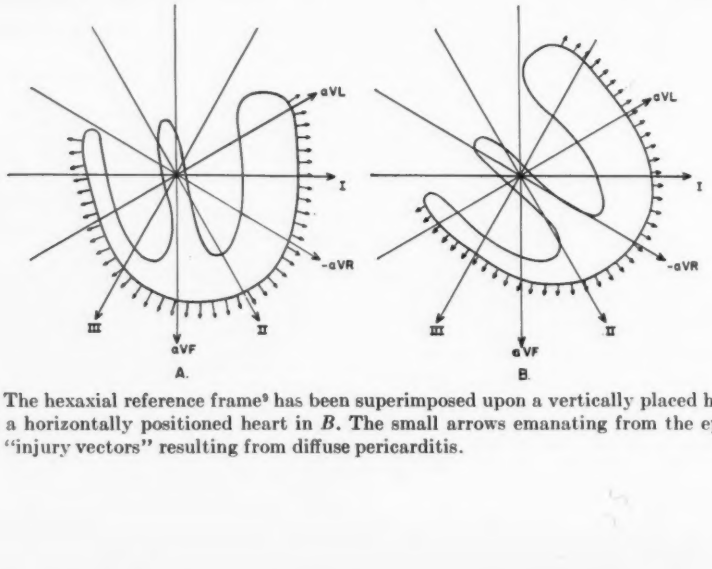

FIG. 1. The hexaxial reference frame[9] has been superimposed upon a vertically placed heart in *A*, and upon a horizontally positioned heart in *B*. The small arrows emanating from the epicardium represent "injury vectors" resulting from diffuse pericarditis.

variable degree. Since these respective systolic and diastolic potential differences have opposite polarities, they summate to increase the divergence between the 2 segments. In electrocardiographic terminology this divergence is referred to as S-T segment displacement.

The occurrence of S-T elevation in a particular lead depends upon the axis of the lead, the position of the heart, and the extent of the pericarditis. In the case of the extremity leads these relationships are illustrated in figure 1, where it is assumed that the inflammatory process involves the epicardial surface *diffusely*. The leads, represented as vectors, of the hexaxial reference frame in which lead aV_R is considered to have a polarity opposite to that with which it is usually recorded[9] are superimposed on a vertically placed heart in *A* and on a more horizontally positioned heart in *B*. The differences in potential between the inflamed epicardium and adjacent myocardium, accounting for the different levels at which the S-T and T-P segments are inscribed, are represented by "injury vectors" radiating out from the periphery of the epicardial surface. Coincidence of direction of lead axis and an injury vector component contributes to the inscription of S-T elevation, whereas divergence of direction contributes to S-T depression. The sum total of the components of all of the injury vectors projected on the lead axis determines the direction and the degree of S-T segment shifted recorded in that particular lead. Therefore, regardless of heart position, leads II and $-aV_R$ usually demonstrate substantial degrees of S-T elevation. In the vertical heart position lead aV_F records the components of a larger number of injury vectors producing S-T elevation than does lead I, whereas, in the horizontal heart position, these relationships are reversed. In the vertically placed heart, lead III demonstrates S-T elevation whereas, in the horizontal heart, figure 1*B* illustrates the reason for the frequency of an isoelectric or perhaps slightly depressed S-T segment in this lead. Similarly, in the case of lead aV_L, an isoelectric or slightly depressed S-T segment may occur in the vertical heart position, whereas an elevated S-T segment is to be expected in a more horizontally placed heart. It should be realized that the manner in which pericarditis alters S-T segments in various leads has been greatly simplified in figure 1, but this scheme may be contrasted with the effect of *localized* epicardial and subepicardial injury resulting from narrowing or occlusion of a branch of a coronary artery. If, in the latter condition, a lead axis passes through or adjacent to the injured area with such a polarity that the injury vectors project sufficient components upon the lead to cause the inscription of S-T depression, these components are not canceled or exceeded by those of oppositely directed injury vectors arising from the epicardial region of the opposite side of the heart. Thus, in myocardial infarction, leads I and aV_L tend to demonstrate segment shift that is displayed in the opposite direction in leads III and aV_F, regardless of heart position. Since apical infarction is relatively rare, leads II and $-aV_R$, whose axes point in a general direction from base to apex, usually show less marked segment shift than the other 4 extremity leads, whereas in *diffuse* pericarditis, II and $-aV_R$ are the leads whose S-T segments are most frequently and markedly elevated.

The wide distribution of S-T segment elevation in precordial leads commonly seen with pericarditis in contrast to the localized distribution of S-T elevation or concomitant occurrence of S-T elevation and depression with infarction, may be explained by applying the principles already enumerated for the limb leads although one must be more cognizant of the importance of proximity effects.

In most cases, S-T segment deviation results from direct injury to the epicardial region by the agent responsible for the pericarditis. It has been shown experimentally, however, that S-T elevation can be produced by injection of innocuous substances, such as warm saline and serum, into the pericardial sac, the apparent mechanism being compression and resultant ischemia of the epicardial muscle layer.

A normally upright T wave represents the

spread of the repolarization process in the general direction from epicardium to endocardium. Since inverted T waves commonly develop with pericarditis in those leads in which elevated S-T segments had previously occurred, it may be postulated that the duration of the repolarization in the previously injured epicardial muscle layer is sufficiently lengthened to bring about a net reversal of the direction of this process. This explanation is in line with the finding that the Q-T interval may be increased at this time.

Physician: Is there any characteristic ballistocardiographic pattern in pericarditis?

Dr. Kotte: There is no characteristic pattern. We have observed normal ballistocardiograms during the course of acute nonspecific pericarditis when the electrocardiogram showed typical alterations. However, nonspecific abnormalities may occur. The ballistocardiograph has not been studied sufficiently in nonspecific pericarditis to furnish adequate data concerning the incidence of such abnormalities or to determine whether they correlate with clinical evidence of cardiac tamponade or myocardial dilatation. At the present time the possible potential usefulness of this instrument in the differentiation of acute pericarditis from myocardial infarction is purely speculative.

Dr. McGuire: We believe our third case is of interest since it may represent an example of the syndrome recently described by Dressler.[10]

Case 3

On January 16, 1954, a 51-year-old white man was admitted to the hospital because of the onset of severe precordial pain with radiation into the left arm accompanied by profuse diaphoresis. Physical examination revealed a pulse rate of 120 and slight cyanosis of the lips. There was no cardiac enlargement, and no murmurs or friction rubs were heard. An electrocardiogram revealed an extensive acute anteroseptal myocardial infarct.

The initial pain was controlled with morphine. After the third day he was free of pain. Anticoagulant therapy was started.

During the last week of January the patient complained of aching in the left shoulder region. The temperature rose to 100.8 F., and slight tachycardia developed. A pericardial friction rub was heard over the lower sternum. The aching pain in the lower left chest was accentuated by deep breathing. The white count rose to 19,000 with 76 per cent neutrophils. The prothrombin time had fallen to 6 per cent of normal, and dicumarol was temporarily discontinued. A portable x-ray of the chest showed slight left pleural effusion and marked cardiac enlargement. Physical examination suggested pericardial effusion. By the end of the first week in February, the patient felt well again. Chest x-ray showed the heart size to be normal. The pleural effusion had disappeared. Convalescence was uneventful and by March 1 he felt entirely normal. Electrocardiograms showed a stabilized pattern of anteroseptal myocardial infarction. He was discharged and while at home felt well until the twelfth of March when he developed aching pain in the left shoulder and arm. The pain occasionally radiated into the left part of the neck. The substernal sharp pain was definitely aggravated by movement and deep inspiration and temporarily relieved by sitting up. The temperature was 100.3 F. Physical examination revealed a to-and-fro friction rub over the precordium and a loud pleural friction rub over the left lower anterior chest.

He was readmitted to the hospital. An electrocardiogram showed slight elevation of S-T segments of V_2 and V_3 in addition to the typical changes of anteroseptal myocardial infarction. Chest x-rays demonstrated pleural effusion at the left base without cardiac enlargement. The prothrombin time was 21 per cent. Because of the possibility of bleeding into the pericardial cavity and pleural space, dicumarol was discontinued. By March 18 the patient had greatly improved and the pericardial friction rub had disappeared. The sedimentation rate was 48 mm., white blood count 9,000, with 60 per cent neutrophils. Electrocardiograms showed no evidence of a new infarct. He was discharged April 1 and has continued to be asymptomatic.

Dr. Ralph Scott: This patient had 2 distinct bouts of pericarditis and pleurisy during the second and eighth week of his convalescence from an acute myocardial infarction. Complications such as these are commonly attributed either to an extension of the area of myocardial infarction or to pulmonary infarction. However, there was no evidence of either, in that the electrocardiogram remained stable, the effect of change in position and respiration on the pain was not characteristic of myocardial ischemia, and there was no hemoptysis nor any evidence of thrombosis of the leg veins. With the first episode the rapid change in the size of the cardiac silhouette in the absence of clinical and x-ray evidence of pulmonary congestion strongly suggested peri-

cardial effusion rather than cardiac dilatation. Massive effusion with pericarditis resulting from epicardial infarction is uncommon unless, with anticoagulant therapy, bleeding from the infarcted area occurs. The possibility of hemopericardium and hemothorax complicating the excessively prolonged prothrombin time was considered, but it seemed unlikely that bleeding would occur into 2 separate serous cavities in the absence of both microscopic hematuria and hemorrhagic manifestations in skin and mucous membranes. The clinical manifestations, particularly their recurrent nature, were most reminiscent of acute nonspecific pericarditis, and this diagnosis was strongly entertained. Dressler[10] has since described a postmyocardial infarction syndrome characterized by recurrent febrile manifestations of pericarditis, pleurisy, and pulmonary inflammation, mimicking those of nonspecific pericarditis, and we feel that our case falls into this category. Of Dressler's 10 reported cases, 8 were observed during a period of 13 months in a single hospital, this incidence being greater than that of uncomplicated nonspecific pericarditis in the same hospital over the same period. This fact led Dressler to conclude that the chance coincidence of myocardial infarction and nonspecific pericarditis is unlikely. With the increased recognition of the postinfarction syndrome, which will undoubtedly occur as the result of Dressler's excellent contribution, a larger statistical study of its incidence in relation to that of spontaneously occurring nonspecific pericarditis would be of interest.

Physician: What is known concerning the cause of acute nonspecific pericarditis, of the pericarditis of the post commissurotomy syndrome, and of the postinfarction pericarditis described by Dressler?

Dr. McGuire: Both Burchell[2] and Wolff[11] believe that there is no single cause for acute nonspecific pericarditis but that a number of different agents are responsible for this peculiar disorder.

The notorious frequency of relapse in nonspecific pericarditis, the fever, leukocytosis, and increased sedimentation rate strongly suggest an infectious etiology. However, the agent or agents causing acute nonspecific pericarditis have not been identified. The frequency of upper respiratory infections preceding the onset of this form of pericarditis is reminiscent of respiratory infections preceding the onset of acute glomerulonephritis and of rheumatic fever. However, no consistent elevation of the antistreptolysin or antihyaluronidase titers has been noted in patients with acute nonspecific pericarditis, nor have throat cultures in the few reported cases shown any marked predominance of streptococci. The few cultures reported from the pericardial fluid have been sterile. Sera from 5 children with acute nonspecific pericarditis have been negative for cold antibodies and for antibodies to the viruses of influenza A and B, lymphogranuloma venereum, psittacosis, Q fever, and to several strains of Coxsackie virus.[12] Pericarditis mimicking acute nonspecific pericarditis has occurred during the course of infectious mononucleosis.

The clinical pictures of pericarditis in the postcommissurotomy syndrome and in acute nonspecific pericarditis have much in common although the arthralgias of the postcommissurotomy syndrome are not present in acute nonspecific pericarditis. Whether the pericarditis following mitral valve surgery is due to activation of latent rheumatic fever or to an unknown etiologic agent is not known.

The peculiar pericarditis following myocardial infarction described by Dressler[10] closely resembles acute nonspecific pericarditis and may in fact be caused by the same agent or agents responsible for acute nonspecific pericarditis. It is interesting to speculate whether trauma by the surgeon or by a myocardial infarction may play a similar role in the causation of pericarditis.

Dr. McGuire: The primary purpose of this conference has been to call attention to the relative frequency with which acute nonspecific pericarditis is erroneously diagnosed as acute myocardial infarction. This has unfortunate implications, both from a therapeutic standpoint, since anticoagulants are contraindicated in pericarditis, and also from a

prognostic standpoint because the diagnosis of infarction has important economic and social ramifications. The first 2 cases represent instances of such mistaken diagnoses that could have been avoided on the initial examinations by careful evaluation of certain differential diagnostic points. It is possible that, in the future, serial estimations of the serum transaminase reaction[13] may prove to be a distinct laboratory aid in the differentiation of these 2 conditions. The third case was presented to illustrate a new syndrome recently described by Dressler in which an apparently benign form of pleuropericarditis complicates myocardial infarction.

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Fair, E.: Resuscitation after Fifty Minutes of Cardiac Arrest. Am. J. Surg. **90:** 419 (Sept.), 1955.

The author discussed the subject of cardiac arrest and reported 3 illustrative cases, 1 being a successful resuscitation after 50 min. of asystole.

It was pointed out that cardiac arrest is a much more frequent occurrence than is generally realized. The data collected from the literature also indicate that the actual incidence of this condition is increasing. Most cardiac arrests are preventable if attention is paid to the preoperative preparation of the patient. During the operation, the most important prophylactic measure is anesthetic management, particularly the maintenance of adequate oxygenation.

Treatment resolves itself into the main purposes of early oxygenation of tissues, especially the brain, and production of blood flow by cardiac massage until normal heart beat is restored. As adjunct therapy, intracardiac epinephrine, barium chloride, and whole blood, in the presence of hemorrhage, are worthy of trial. For ventricular fibrillation, cardiac massage, procaine amide and electric shock to produce defibrillation, are indicated.

Abramson

ABSTRACTS

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BACTERIAL ENDOCARDITIS

Wallach, J. B., Glass, M., Lukash, L., and Angrist, A. A.: The Distinctive Nature of Bacterial Endocarditis in Patients Over 50. Geriatrics **11:** 35 (Jan.), 1956.

In a study of a series of 8,676 consecutive autopsies reviewed from 1936 through 1950, 509 (5.9 per cent) were classified as rheumatic heart disease, and bacterial endocarditis was found in 82 (16.1 per cent) of the rheumatic patients. Bacterial endocarditis, superimposed on rheumatic heart disease, was more often acute in the older subjects. Thus, in those with underlying rheumatic heart disease, bacterial endocarditis was acute in 7, or 53 per cent, of 13 older persons but in only 14, or 20 per cent, of 69 younger persons. In those without underlying rheumatic heart disease, the endocarditis was acute in 13 of the 17 aged subjects, or 76 per cent, as compared to at least 24 of 30, or 80 per cent, under 50. As might be expected, the underlying pathology was usually that most common in each age group. Thus, younger persons had underlying rheumatic, syphilitic, or congenital heart disease or lupus erythematosus, whereas older subjects most often showed sclerotic changes in the valves. In the younger individuals, the disease occurred more often following dental manipulation or abortion, but, in the older subjects, it was found more frequently in the postoperative state. Acute endocarditis in those under 50 was associated with a severe primary infection, such as lobar pneumonia or meningitis. In the aged the most common associated diseases were infection of the genitourinary system; bronchopneumonia, usually secondary; malnutrition; and diabetes. The bacteria responsible in the older group were more commonly of the septic variety and frequently originated in the genitourinary system. Such valve lesions were often acute and ulcerative. *Streptococcus viridans* was the most frequent organism recovered in younger subjects, particularly in those with underlying rheumatic heart disease. Thus valve lesions in this group were more often of the classical subacute bacterial variety. In younger individuals, especially in those with underlying rheumatic heart disease, bacterial endocarditis was the significant cause of the illness and death. However, in the aged group, the endocarditis was often only an incidental, terminal lesion, contributing little to the clinical course or primary cause of death. Glomerular lesions were less common in the aged.

RINZLER

BLOOD COAGULATION

Littman, J. K., and Brodman, H. R.: Surgery in the Presence of the Therapeutic Effect of Dicumarol. Surg., Gynec. & Obst. **101:** 709 (Dec.), 1955.

A study was made on 60 patients subjected to operative procedures, some of whom were receiving anticoagulants concomitantly with surgery. From the results the authors concluded that it is generally feasible to operate upon a patient treated with dicumarol. However, the prothrombin time should not be prolonged for more than 70 sec. In such a situation coagulation does occur but is delayed.

ABRAMSON

Manson, D. I., and Fullerton, H. W.: Anticoagulant Therapy in Cardiac Infarction. Brit. M. J. **1:** 6 (Jan. 7), 1956.

Anticoagulant therapy with ethyl biscoumacetate greatly reduced the incidence of thromboembolic complications and the mortality rate in a group of

102 cases of myocardial infarction. Prolonged therapy with intramuscular heparin was without notable effect in 62 cases. As far as selection of cases is concerned, "electrocardiographic confirmation of the clinical diagnosis has not been regarded as essential in all cases included in the survey." Controls consisted of patients admitted to the Woodend Hospital in Aberdeen; the treated series was observed at the Aberdeen Royal Infirmary.

In the series of 102 cases given anticoagulant therapy 8 (7.8 per cent) died, whereas 15 of 62 cases (24.2 per cent) receiving intramuscular heparin died and 45 of 150 cases (30 per cent) receiving no anticoagulant died.

McKusick

CONGENITAL ANOMALIES

Cooley, D. A., and Mahaffey, D. E.: Anomalous Pulmonary Venous Drainage of Entire Left Lung: Report of Case with Surgical Correction. Ann. Surg. **142:** 986 (Dec.), 1955.

The authors reported a case of a 29-year-old white man complaining of palpitation and fatigue, who on x-ray demonstrated enlargement of the right ventricle and undivided pulmonary artery. Both the right and left pulmonary arteries were dilated and pulsated vigorously in fluoroscopy. There was an unusual irregular shadow in the left superior mediastinum, giving the appearance of a "figure of eight" deformity.

At operation the right atrium and superior vena cava were found to be distended and contained bright red blood. The right pulmonary artery and veins were dilated, and a large, thin-walled anomalous vein was seen originating on the superior and posterior aspect of the left pulmonary hilum and emptying above in the left innominate vein. This vessel was ligated at the junction with the innominate vein and divided, and an anastomosis was performed between the cut end and the left atrium. The postoperative course was uneventful.

Abramson

O'Sullivan, W. D., and Glenn, F.: Contraindications to the Surgical Therapy of Coarctation of the Aorta. Ann. Surg. **142:** 909 (Dec.), 1955.

The contraindications for operative treatment of coarctation were reviewed by the authors and case reports were presented to illustrate the various points. They stated that patients in whom life expectancy would be of normal length without operation are not suitable candidates. This would generally apply to the fully mature adult in whom the blood pressure proximal to the coarctation is normal or near normal and there is a good pulse pressure in the lower extremities, with no evidence of collateral circulation. It is much more difficult to determine whether a young person will have a normal length of life expectancy without operation.

Other contraindications to operation are aortic lesions not suitable for operative correction and serious co-existing disease. In the absence of definite cause, operation may be safely deferred until 8 years of age. Patients beyond the age of 40 present an increased risk, technical difficulties at the time of operation, and a lesser likelihood of reversion to normality.

Abramson

Silverman, B. K., Nadas, A. S., Wittenborg, M. H. Goodale, W. T., and Gross, R. E.: Pulmonary Stenosis with Intact Ventricular Septum. Correlation of Clinical and Physiologic Data, with Review of Operative Results. Am. J. Med. **20:** 53 (Jan.), 1956.

Data on fifty patients with proved pulmonary stenosis and intact ventricular septum are presented. The main symptoms included severe dyspnea and fatigue with mild, if any, cyanosis. About 25 per cent of the patients were asymptomatic. The characteristic findings included a rough systolic murmur with a diminished second sound at the upper left sternal border, evidence of right ventricular hypertrophy in the electrocardiogram, and right ventricular enlargement, prominent main pulmonary artery, and diminished pulmonary vasculature in roentgenograms. Physiologic data reveal varying degrees of right ventricular hypertension and a systolic gradient across the pulmonary valve. The pressure tracings generally suggest valvular stenosis. Arterial unsaturation at rest always indicates severe stenosis and is found in about 10 per cent. A significant correlation between the electrocardiographic findings of right ventricular hypertrophy and right ventricular systolic pressure could be established in this series. All 20 patients with a right ventricular pressure of 100 mm. Hg or more showed 1 of several of the following electrocardiographic changes: (1) an R wave in V_{4R} or V_1 of 20 mm. or over; (2) "P Pulmonale"; (3) abnormal right-sided S-T segment and T-wave changes.

Three fatalities, all in patients with failure, occurred among the 21 patients subjected to Brock valvotomy. All survivors improved clinically. A satisfactory drop in right ventricular pressure was achieved in 7 of 8 patients catheterized postoperatively.

A therapeutic classification is proposed: 1. Infants with severe stenosis in congestive failure should be operated on as soon as the diagnosis is made. 2. Patients with clinical findings suggesting right ventricular pressures of 100 mm. Hg or over usually should be operated on at an appropriate time. 3. Patients in whom findings indicate a right ventricular pressure under 100 mm. Hg should be observed carefully, but need not be subjected to cardiac catheterization or to operation.

Harris

Miettinen, M., Hakkila, J., and Sepilä, W.: Coarctation of the Abdominal Aorta and Report of a Case with Three Pregnancies. Ztschr. Kreislaufforsch. **45:** 33 (Jan.), 1956.

A case is reported of a 37-year-old woman who since childhood has complained of cold sensitivity and tiredness in the lower extremities. Of 3 pregnancies, the first terminated in abortion, the second in premature delivery in the seventh month, and the third had a normal course. The blood pressure was considerably higher in the arms than in the legs. A systolic thrill was palpable, and murmurs, audible in the epigastrium, radiated to the back. Delay of the femoral pulse wave was demonstrable in sphygmograms and the ballistocardiogram revealed features characteristic of coarctation. This was confirmed at laparotomy and it involved the entire abdominal aorta so that a surgical repair was not considered feasible. A unilateral hydronephrosis and hydroureter were present in addition.

The literature dealing with abdominal coarctation is reviewed with reference to incidence, symptomatology, differential diagnosis, and operability. Differences in sex distribution when compared with ordinary coarctation are pointed out.

PICK

Smart, J., and Pattinson, J. N.: Congenital Absence of Left Pulmonary Artery. Brit. M. J. **1:** 491 (Mar. 3), 1956.

The authors report a 30-year-old man who was referred because of peculiar findings on routine mass miniature x-ray examination: smaller left lung, moderate displacement of mediastinum to left, right pulmonary artery of larger appearance than normal. The patient was completely asymptomatic with no abnormalities on physical examination. Bronchograms were normal. The aortic arch was on the right. The electrocardiogram was normal. Angiocardiogram showed no left pulmonary artery. Bronchospirometry showed about equal ventilations (left 2,350 ml.; right 2,800 ml.). There was, however, no oxygen uptake from the right side.

MCKUSICK

Rossi, E., Holzmann, M., Hedinger, C., and Buhlmann, A.: Cyanotic Cardiac Lesions with Pulmonary Hypertension. Cardiologia **28:** 131 (Fasc. 3), 1956.

An unusual case is described of a 16-year-old girl who up to 15 years had no significant symptoms or signs of cardiovascular disease. At this age she developed progressive cyanosis and dyspnea, a systolic and diastolic murmur over the apex, and a loud second sound with a diastolic murmur in the pulmonary area. The electrocardiogram showed pronounced right heart strain, the x-ray a prominent pulmonary arterial segment in the presence of small hili and reduced pulmonary vascular markings. At cardiac catheterization a pulmonary vein was entered via the left atrium and revealed normal oxygen saturation. Right ventricular and pulmonary arterial pressures were equally high (120/0 and 125/75 mm. Hg respectively) and the peripheral arterial blood was desaturated to 84 vol. per cent. Selective angiocardiography through the catheter showed a normal origin of the aorta and pulmonary artery. On that basis the diagnosis of an atrial septal defect with pulmonary hypertension was made clinically.

The patient died from progressive right heart failure and autopsy revealed a pulmonary valvular stenosis with marked dilatation of the pulmonary artery, a patent foramen ovale, parietal thrombosis in the dilated right ventricle and numerous emboli and infarcts of various age in both lungs. The development of pulmonary hypertension, which apparently abolished a pressure gradient across the pulmonary valve and caused regurgitation by dilating the pulmonary artery, is ascribed to the thromboembolic processes in the lungs.

PICK

Siegenthaler, W.: Cardiovascular Alteration in Marfan's Syndrome (Arachnodactylia). Cardiologia **28:** 135 (Fasc. 3), 1956.

Based on 5 personal observations the symptomatology of Marfan's syndrome is described with special reference to its cardiovascular manifestations. The author draws attention to the "formes frustes" of the syndrome manifested by isolated anomalies of the aorta, in particular aortic aneurysm in younger persons and the so-called idiopathic dilatation of the pulmonary artery, the several varieties of cardiac hypertrophy of obscure etiology, various congenital malformations of the heart and cardiovascular anomalies associated with funnel chest and kyphoscoliosis.

PICK

Espino-Vela, J., and Castro-Abreu, D.: Congenital Heart Disease Associated with Pregnancy: A Study of 53 Cases. Am. Heart J. **51:** 542 (Apr.), 1956.

Fifty-three cases of congenital heart disease associated with pregnancy were studied. The material consisted of 28 cases of patent ductus arteriosus, 13 cases of atrial septal defect, 6 cases of coarctation of the aorta, 2 cases of ventricular septal defect, and 1 case of each of the following: tetralogy of Fallot, dextrocardia with situs inversus, pulmonic stenosis, and aortic stenosis. This series includes 4 deaths directly attributable to pregnancy. Three took place in patients with patent ductus arteriosus, 2 of whom had a window-type ductus. The other took place in a patient with an atrial septal defect. Tolerance to the congenital malformation prior to pregnancy is a useful guide in the prognosis of the pregnant period. In cases of patent ductus arteriosus, the size of the ductus would appear to

be of primary importance, as this is ultimately expressed in magnitude of blood flow through the ductus. Should this flow be excessive, cardiac reserve is threatened when a new arteriovenous fistula, the placental, is added. This latter fistula adds its adverse effects to those of the ductus. In atrial septal defects pregnancy seems to tax cardiac reserve when, due to the presence of the malformation, the right cavities suffer considerable overloading during pregnancy, at which time the arteriovenous shunt is reversed, with all its unfavorable consequences. Aortic coarctation, although benign in this short series, is to be considered one of the greatest risks in pregnancy, as pointed out by numerous workers. The malformation in the mother seems to have very little, if any, influence on the infant. In this series, bacterial endarteritis was encountered 3 times in cases of patent ductus arteriosus and 1 of these patients died as a direct consequence of this complication after childbirth. This is a strong argument in favor of operating upon every case of patent ductus arteriosus. Pregnancy per se, if the condition of the patient is not critical and yet merits an operation, is not a normal contraindication for surgery. Eleven patients have been operated upon in this series; 9 with patent ductus arteriosus, 1 with atrial septal defect, and 1 with the tetralogy of Fallot. At the present time practically all the patients could be included among candidates for surgery for correction of their heart malformation, either partial or radical. Cesarean section, with the exception of cases of aortic coarctation, has very limited indications and should be reserved for gynecologic problems.

RINZLER

Bowers, D., Swan, H. J. C., and Burchell, H. B.: Left-to-Right Extracardiac Shunts in the Presence of Pulmonary Stenosis. Am. Heart J. **51:** 568 (Apr.), 1956.

The clinical and hemodynamic data from 4 patients, each with pulmonary stenosis and a congenitally patent aortopulmonary communication, have been contrasted with respect to the presence or absence of coexisting ventricular septal defects and veno-arterial shunts. The aortopulmonary communication in 1 patient was shown to result from a supravalvular aortopulmonary window, and in another patient, from enlarged bronchial arteries. In each of the remaining 2 patients, a patent ductus arteriosus was believed to have formed the aortopulmonary communication. In 2 patients, the pulmonary stenosis and aortopulmonary shunts were complicated by ventricular septal defects. In each of these 2 patients, the blood flowing across the aortopulmonary communication fulfilled a useful purpose and may have compensated for the reduced flow of blood across the pulmonary valve, because of a venoarterial shunt at the ventricular level. In each of the 2 patients without associated ventricular septal defects, the flow of blood across the aortopulmonary communication (patent ductus arteriosus) imposed an uncompensated burden on the left ventricle. For such patients, the treatment of choice is closure of the patent aortopulmonary communication and relief of the obstruction in the outflow tract of the right ventricle.

RINZLER

Kraemer, W. F., Gensini, G., Blount, S. G., Jr., and Lanier, R. R.: Roentgen Aspects of Atrial Septal Defect, Ostium Secundum. Acta Radiol. **44:** 441 (Dec.), 1955.

The wide variation of the roentgenographic characteristics of 20 cases of atrial septal defect of the secundum type, proved by direct visualization at the time of operation, are presented. The lack of correlation of the findings with each other and with hemodynamic factors (cardiac catheterization data) is stressed. One half of the cases had pulmonary arterial pressures either slightly elevated or completely within the normal range.

The most reliable criteria were (1) increased vascularity of the lungs, (2) enlargement of the main pulmonary artery and its branches, (3) enlargement of the right atrium, (4) normal left heart chambers, and (5) a normal or small aorta. It is often impossible to distinguish this condition from other left-to-right shunts without supplementary (catheterization and angiocardiography) aids.

SCHWEDEL

Welsh, R. A., and Felson, B.: Uncomplicated Dextroversion of the Heart. Radiology **66:** 24 (Jan.), 1956.

The authors report on the roentgenologic features in 6 cases of uncomplicated dextroversion of the heart. Rotation along the vertical axis occurs so that the left ventricle presents anteriorly, the right ventricle on the right side, the right atrium posteriorly, and the left atrium on the left. The aorta and the pulmonary artery are relatively normal in position, and the aortic knob generally presents on the left with its indentation of the barium-filled esophagus as is usual in normal individuals. Slight rotation of the patient often restores an almost normal P-A cardiac appearance.

SCHWEDEL

Burroughs, J. T., and Kirklin, J. W.: Complete Surgical Correction of Total Anomalous Pulmonary Venous Connection: Report of Three Cases. Proc. Staff Meet., Mayo Clin. **31:** 18[illegible] (Mar.), 1956.

Three cases of total anomalous pulmonary venous connection in which corrective operations have been performed are discussed in detail. Surgical technic and pertinent physiologic data are given. In all 3 cases there was evidence of complete correc

t on of the anomaly. There was 1 postoperative d ath. The remaining 2 patients are completely c ired of their gross cardiac abnormality.

A summary of the pertinent diagnostic data ob- t ined at cardiac catheterization preoperatively a d postoperatively in these patients is presented. I reoperatively the blood oxygen saturation was e qual in the right ventricle and in the peripheral a terial system in 2 patients. In a third patient the l lood oxygen saturation was higher in the pul- m onary artery than in the systemic artery. These f ndings are characteristic of the anomaly. When s ch a degree of arterialization is found at atrial l vel it should be emphasized that the diagnosis of t tal anomalous pulmonary venous connection c nnot be made, since a functionally common atrium without anomalous pulmonary venous connection can produce the same physiologic situation. Thus the diagnosis of total anomalous pulmonary venous drainage is made under these conditions. In 1 patient the point of arterialization at the level of the superior vena cava, plus the roentgenologic finding of the widened supracardiac mediastinal shadow, made possible the diagnosis of total anomalous pulmonary venous connection. The postoperative data obtained in each patient demonstrated complete correction of the abnormal flow.

SIMON

DuShane, J. W.: Total Anomalous Pulmonary Venous Connection: Clinical Aspects. Proc. Staff Meet., Mayo Clin. **31:** 167 (Mar.), 1956.

The clinical findings produced by complete anomalous pulmonary venous connection in infants depend on the anatomic situation and the resultant hemodynamic events. Pulmonary venous blood enters the right atrium either directly or via a tributary of the right atrium; thus the right atrium receives all of the pulmonary venous blood as well as the systemic venous blood. A large portion of this mixture usually enters the right ventricle through the tricuspid valve and flows into the pulmonary artery, resulting in an increase in pulmonary blood flow. The left atrium and left ventricle receive only the amount of blood that passes through the foramen ovale or an atrial septal defect. If the foramen ovale is small or if the valve covering it begins to close, the volume of blood reaching the left side of the heart becomes even smaller. If the pulmonary venous connection to the systemic venous system is small or follows a devious route, pulmonary congestion and eventual pulmonary arterial hypertension result.

The clinical diagnosis of complete anomalous pulmonary venous connection in infants can be suspected if the symptoms, signs, and roentgenologic and electrocardiographic features are carefully assessed and properly interpreted in relation to the hemodynamic changes that occur. Of a total of 506 infants and children with congenital heart disease studied in the past 2 years, 8 have had complete anomalous pulmonary venous connection as proved by cardiac catheterization, operation, or necropsy. In 5 of the 8 patients the proper diagnosis was suspected clinically. Prior to 1954 this diagnosis was made in infants only at necropsy. This improved accuracy of clinical diagnosis is evidence of an increased awareness of this condition and reflects the progress that has been made in correlating anatomic and physiologic principles with their clinical manifestation in the field of congenital heart disease.

SIMON

Edwards, J. E., and Helmholz, H. F.: A Classification of Total Anomalous Pulmonary Venous Connection Based on Developmental Considerations. Proc. Staff Meet., Mayo Clin. **31:** 151 (Mar.), 1956.

"Total anomalous pulmonary venous connection" is an anatomic term used to designate any major deviation in development affecting the entire pulmonary venous system. It is particularly important to understand the nature of these anomalies when surgical correction is being contemplated. Among the cases so designated anatomically, functionally there are examples with no shunts, shunts of bidirectional nature, left-to-right shunts, and right-to-left shunts.

From relatively simple differences in details of development, diverse gross anatomic pictures may result. Depending, in part, on differences in the final anatomic picture, there results a wide spectrum of functional disturbances in total anomalous pulmonary venous connection. Only 1 of these disturbances is total anomalous pulmonary venous drainage.

SIMON

Donzelot, E., Serafini, V., Bougnoux, J., Kervoelen, and De Balsac, R. H.: Radiological Kinetics and Pulmonary Arterial Pressure in Congenital Heart Disease. Brit. Heart J. **18:** 35 (Jan.), 1956.

The technics of electrokymography and cardiac catheterization were used to register the movements and intravascular pressures of the pulmonary artery in 13 individuals with pulmonary stenosis, 8 with Fallot's tetralogy, 15 with atrial septal defects, 2 with patent ductus, and 2 with Eisenmenger's complex. The form of the normal pulmonary electrokymogram can almost be superimposed upon that of the pulmonary artery pressure curve.

In pulmonary stenosis, the curves are modified according to the degree and type of stenosis and return toward normal after successful valvotomy. The electrokymogram is reduced in amplitude and the initial upstroke is delayed and slower in ascent. The arterial character of the curve is completely lost in infundibular or combined infundibular and valvular stenosis. The pulmonary artery pressure

curve is slightly delayed and is also reduced in amplitude.

In patent ductus, both curves are superimposable and show a rounding of their summits and an early diastolic rebound.

In atrial septal defect, the electrokymogram is of high amplitude and frequently shows a double diastolic rebound. The pressure curves may show a rounded summit and a double diastolic rebound. There appears to be an inverse relation between level of pressure and size of pulsations.

In Eisenmenger's complex, the electrokymogram shows a horizontal plateau in the second half of systole. The pressure curve shows a prolonged systole with an early diastolic notch. The diastolic downstroke is at first steep and then gradual.

SOLOFF

CORONARY ARTERY DISEASE

Gilchrist, A. R., and Tullock, J. A.: An Evaluation of Anticoagulant Therapy in Acute Myocardial Infarction. Scottish M. J. **1:** 1 (Jan.), 1956.

The authors review statistics that they interpret as indicating a halving of anticipated mortality rate during the first 6 weeks, with a comparable reduction in incidence of thromboembolic episodes, when anticoagulants are employed. They believe that there is much to recommend limiting their use to "good risk" cases but lament the inadequacy of clinicians in evaluating risk in the early stages of the illness.

An autopsy series of 248 fatal cases (88 received anticoagulant treatment) failed to reveal a reduced incidence of intraventricular thrombi or of peripheral arterial emboli, but did reveal a reduction in the incidence of pulmonary infarction in the treated group.

The authors believe the risk of hemorrhagic complications has been greatly exaggerated. However, there is distinct necessity for laboratory control on therapy.

MCKUSICK

Wachtel, F. W., and Teich, E. M.: Tall Precordial T Waves as the Earliest Sign in Diaphragmatic Wall Infarction. Am. Heart J. **51:** 91 (Jan.), 1956.

Two cases are presented in which the earliest electrocardiographic evidence of myocardial infarction was tall, sharply pointed T waves in precordial leads V_2 to V_5. The authors believe that these changes are indicative of ischemia of the diaphragmatic and posterior portions of the left ventricle and are reciprocal reflections of T-wave inversions.

RINZLER

Kennamer, R., and Prinzmetal, M.: Myocardial Infarction Complicated by Left Bundle Branch Block: Studies on the Mechanism of Ventricular Activity. XI. Am. Heart J. **51:** 78 (Jan.), 1956.

Experimental studies to observe electrocardiographic changes in the QRS complex were carried out in 9 dogs by cutting the left branch of the bundle of His from 4 days to 4 weeks after ligation of the anterior descending artery. Histologic examination revealed either subendocardial, through-and-through, or patchy infarctions. In patients with bundle-branch block, the development of myocardial infarcts involving large amounts of subepicardial muscle may be manifest by a decrease in the magnitude of the R wave in precordial leads overlying the left ventricle or aV_F. The value of preinfarction tracings for comparison is discussed. Acute myocardial infarction in the presence of left bundle-branch block is frequently manifest in patients by S-T elevation in the precordial leads overlying the left ventricle or aV_F. In the presence of coronary artery disease, S-T segment changes may occur despite the presence of left bundle-branch block. With exercise or with spontaneous coronary failure, S-T segment depression occurs in those leads overlying the left ventricle or aV_F, and RS-T elevation occurs in those leads overlying the right ventricle. The S-T elevation in V_1 through V_3 may be the more obvious change in such circumstances. The S-T segment changes may be detected only if the previous tracings are available for comparison.

RINZLER

CONGESTIVE HEART FAILURE

Elster, S. K., Braunwald, E., and Wood, H. F.: A Study of C-Reactive Protein in the Serum of Patients with Congestive Heart Failure. Am. Heart J. **51:** 533 (Apr.), 1956.

Forty patients manifesting congestive heart failure have been studied with serial serum determinations for C-reactive protein. This abnormal protein was found in 30 instances. No demonstrable difference in age, sex, or race was noted between the 2 groups. In those patients in whom C-reactive protein was present, the congestive heart failure appeared to be more severe. Fever, elevated erythrocyte sedimentation rate, and pulmonary abnormalities were more common in the group in which C-reactive protein occurred. In approximately one half of the group in which C-reactive protein was found, the protein was initially present but disappeared after 1 to 2 weeks of treatment. In 6 patients, the C-reactive protein persisted in the blood throughout the hospital course. Single determinations of C-reactive protein in the blood of patients with congestive heart failure limit the application of C-reactive protein determinations as a measure of rheumatic activity in acute rheumatic fever and in chronic rheumatic heart disease and

as a measure of necrosis in acute myocardial infarction.

RINZLER

Evans, J. M., and Massumi, R. A.: The Long-Term of the Oral Diuretic 3-Chloro-Mercuri-2-Methoxy-Propylurea (Neohydrin) in Ambulatory Patients. Ann. Int. Med. **44:** 124 (Jan.), 1956.

Oral Neohydrin was used as the sole mercurial diuretic in 38 patients with chronic congestive heart failure, and in 2 patients with chronic renal disease, for periods ranging from 8 to 84 weeks. In 25 of the 38 cardiac patients (68.4 per cent) the heart failure was well controlled on average maintenance doses of 2.7 tablets daily. Eight to 12 tablets/day were tolerated for short periods in certain patients. The drug was discontinued in 9 of the 40 subjects (22.5 per cent) because of side effects. Gingivitis and stomatitis developed in 4, all of whom had prior poor oral hygiene. A dermatitis appeared in 2 subjects but did not recur in 1 of these with reinstitution of the drug. Gastrointestinal symptoms accounted for discontinuance in 2 and renal irritation in 1 subject with pre-existing nephrosis. Inadequate diuresis was observed in 1 subject with chronic renal disease and in 4 of the cardiac subjects (12.5 per cent). Of the latter, those with severe recurrent heart failure with fixed hepatomegaly and ascites were the least responsive, possibly on the basis of poor absorption of the mercury. It is concluded that Neohydrin is an effective and reasonably safe oral diuretic in ambulatory patients with mild to moderate congestive heart failure. Side effects are less frequent and less severe in comparison with parenteral mercurials, with the exception of the occurrence of gingivitis in patients with poor oral hygiene.

WENDKOS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, AND BALLISTOCARDIOGRAPHY

Marshall, J. M., and Vaughan Williams, E. M.: Pacemaker Potentials. The Excitation of Isolated Rabbit Auricles by Acetylcholine at Low Temperatures. J. Physiol. **131:** 186 (Jan.), 1956.

Isolated rabbit atria in a chamber at low temperatures (14 to 20 C.) showed cessation of all mechanical and electric activity except small rhythmical potentials in the region of the pacemaker. The addition of acetylcholine (10^{-6} to 10^{-8} gm./ml.) caused propagation of the pacemaker potentials and full atrial contractions. This effect could be potentiated by eserine and abolished by atropine. The conclusion drawn was that the pacemaker region was able to resist cooling to a temperature several degrees below that at which the rest of the atrium ceased to contract. The link between the pacemaker and the surrounding tissue, thus broken by cooling, could be restored by acetylcholine.

AVIADO

Haas, H. G., and Klensch, H.: Critic of Ballistocardiographic Methods. Pflüger's Arch. ges. Physiol. **262:** 107 (Jan.), 1956.

The authors present a critical analysis of the physical characteristics of the many ballistocardiographic technics presently available. Evidence is presented that the more commonly used and more practical instruments have the greatest mechanical error. Only low frequency, relatively force free "elongation" ballistocardiographs should be considered for quantitative studies.

CALABRESI

Finkelstein, D., Gold, H., and Bellet, S.: Atrial Flutter with 1:1 A-V Conduction. Am. J. Med. **20:** 65 (Jan.), 1956.

Atrial flutter with 1:1 conduction constitutes a rare but serious cardiac emergency. The authors review their experience with 6 cases in which the paroxysms of 1:1 atrial flutter were controlled by therapy. One patient died from congestive heart failure without showing any significant cardiac lesion at autopsy. This condition should be suspected in patients with or without clinically detectable heart disease if a tachycardia of 225 to 315 beats/min. develops suddenly and if carotid sinus pressure fails to slow the rate. The diagnosis may be established by electrocardiograms taken before, during, or after therapy. The diagnostic criteria are presented. Atrial flutter with 1:1 A-V conduction must be differentiated from paroxysmal atrial, nodal, and ventricular tachycardia. In most cases the difference in rate between these arrhythmias helps to establish the correct diagnosis.

Digitalis is the drug of choice in the treatment of this arrhythmia. Because of the critical state of the patient, it should be administered parenterally, preferably by vein. Results in 5 of the 6 cases indicate an average digitalis dose is adequate to obtain either a higher degree of A-V block, or conversion to atrial fibrillation or to a normal sinus rhythm. The sixth patient was resistant to very large doses of digitalis administered by various routes. Quinidine and procaine amide may be of value in the occasional patient when digitalis fails.

HARRIS

van Bogaert, A., van Genabeek, A., van der Henst, H., Vandael, J., and Arnoldy, M.: Experimental Left Axis Deviation of QRS Not Due to Positional Changes. Arch. mal. coeur **49:** 1 (Jan.), 1956.

In 50 dogs, localized sections of the left ventricu-

lar wall were infiltrated with 5 per cent cocaine solution; left axis deviation in the frontal plane appeared after infiltration of the posterobasal section in 7 per cent, of the anterolateral section in 34 per cent and of the apicoseptal section in 60 per cent of the cases. Usually this change in the direction of QRS was accompanied by a widening of QRS not exceeding 0.02 sec. and by an opposite change in the T wave. This pattern resembles the left ventricular hypertrophy and "strain" pattern; it is ascribed to block of part of the Purkinje system, which causes the injected section of the myocardium to be activated through other parts of this system, in a different direction. These changes are the more pronounced, the nearer the site of injection is situated to the ventricular septum. After prolonged or repeated infiltration with cocaine, marked widening of QRS occurs; this pattern resembles the left bundle-branch block pattern, and is ascribed to block of all Purkinje strands supplying a section of the myocardium, which is now activated by means of slow myocardial conduction. Both the "hypertrophy" and the "bundle-branch block" patterns can accordingly be produced by lesions that do not involve the ventricular septum.

LEPESCHKIN

Bugaro, L., and DeCastro, B.: The Behavior of the Electrical and Mechanical Systole during Therapeutic Fasting in Cardio-Vascular Failure. Folia cardiol. **14:** 523 (Dec.), 1955.

In 16 cases subjected to a liquid diet of no caloric value for 4 to 6 days, the absolute as well as the corrected Q-T duration increased while the second heart sound occurred earlier with respect to the T wave. These findings may be related to the increase of serum sodium and potassium and decrease in serum calcium that often occurs during this diet, but does not constitute an "energetic dynamic cardiac insufficiency," since the diet resulted in improvement of cardiac failure in all cases.

LEPESCHKIN

De Witte, P. E., and Joossens, J. V.: Multiple Auricular Extrasystoles with Concealed A-V Conduction. Acta. cardiol. **11:** 172 (Fasc. 2), 1956.

A detailed analysis of electrocardiograms is presented in the case of a patient who developed runs of atrial premature systoles in the course of digitalis therapy that disappeared following oral potassium administration. Failure of many of these ectopic impulses to activate the ventricles, and varying P-R intervals of the conducted ones, provided an opportunity to study the responsiveness of the A-V junctional tissues at various points of the ventricular cycle. According to the author's interpretation of numerous consecutively blocked ectopic P waves, 3 phases of the refractory period could be distinguished and expressed in terms of (R-P)-(P-R) relationships. The absolute refractory period during which the premature P waves were completely blocked occupied the first 0.10 sec. of the cycle. It then was followed by a short phase of the concealed A-V conduction during which the premature impulse penetrated into the A-V junction but failed to traverse it; as a consequence one or more subsequent premature impulses were blocked or had a prolonged P-R. The end of this period overlapped with the relative refractory phase characterized by A-V conduction at progressively shorter P-R intervals that terminated 0.37 sec. after onset of the cycle. The data are evaluated statistically but no consideration is given to changes of the refractory period with variations in rate.

PICK

Lamb, L. E., Grosgurin, J. R., and Duchosal, P. W.: Vectorcardiographic Studies of Ventricular Hypertrophy. Cardiologia **28:** 65 (Fasc. 2), 1956.

The problem of vectorcardiographic diagnosis of ventricular hypertrophy was studied in 45 patients by the cube system of Duchosal and Sulzer in comparison with the conventional 12 scalar leads. In each case the absolute QRS area, the mean spatial QRS vector, the absolute QRS magnitude, and the longest instantaneous spatial QRS vector were determined and were expressed in terms of electric moment in order to eliminate individual differences dependent on body size.

Left ventricular hypertrophy was frequently associated with increased voltage of the QRS cycle. However, it was better reflected as an increase of the QRS area, since the former may be due merely to a posterior extension of the QRS loop. The value of scalar lead V_2 in assessing this posterior displacement was emphasized. Marked upward deviation of the vector loop was not a characteristic feature of the left ventricular hypertrophy. A mean QRS-vector projection on the frontal plane of plus 15° was found commonly in uncomplicated hypertension and of plus 40° in aortic valvular disease. In mitral insufficiency the vector loop showed displacement in both anterior and posterior direction, while the latter was not found in pure mitral stenosis. Right ventricular hypertrophy due to congenital heart disease displaced the QRS loop to the right and anteriorly, whereas chronic cor pulmonale caused wide variations of the vectorcardiograms depending on the balance of forces created by both ventricles. The location of the point of origin of QRS vectors was related to, and varied with, the type of ventricular hypertrophy. A method of its determination based on comparison of the transverse (bipolar) lead of a vectorial lead system with scalar lead I was outlined.

PICK

Laham, J.: Bilateral Bundle Branch Block. Cardiologia **28:** 285 (Fasc. 4), 1956.

The author presents a critical review of th

lit rature on bilateral bundle-branch block follow-in analysis of 1 observation. The published cases ca be divided into 2 groups. The first group, repre-se ting "false" bilateral bundle-branch blocks, co sists of cases in which the precordial transition zo ne is shifted to the left or of unilateral lesions of th bundle branches associated with hypertrophy of the contralateral ventricle. True bilateral bundle-b nch block patterns are very rare and are always as ociated with prolongation of the P-R interval. T e form of the ventricular complexes is deter-m ned by the more severely affected bundle branch w ile the less severe contralateral lesion lengthens th A-V conduction time. In a complete set of p ecordial leads a delay of the intrinsicoid deflec-ti n can be demonstrated only on the side of the m re affected bundle branch.

PICK

Stern, E. A., and Tenney, S. M.: Correlation of the Spatial Vectorcardiogram and the Electrocardiogram in Right Ventricular Hypertrophy. Am. Heart J. **51:** 53 (Jan.), 1956.

In order to define the usefulness of the spatial vectorcardiogram as compared with the electrocardiogram in the diagnosis of right ventricular hypertrophy, 30 records were made in 19 patients with chronic pulmonary disease, with and without cor pulmonale, and 8 in patients with right ventricular hypertrophy of primary cardiac origin. The spatial vectorcardiogram may show right ventricular hypertrophy when the standard electrocardiogram shows normal or equivocal findings. The presence of pulmonary emphysema introduces rotational changes in the spatial vectorcardiogram that tend to obscure the electrocardiographic pattern of right ventricular hypertrophy.

RINZLER

Burger, H. C., van Milaan, J. B., and Klip, W.: Comparison of Two Systems of Vectorcardiography with an Electrode to the Frontal and Dorsal Sides of the Trunk, Respectively. Am. Heart J. **51:** 26 (Jan.), 1956.

The tetrahedron system of vectorcardiography proposed by Wilson is compared with a system proposed by the authors. It was found that the agreement between the 2 systems is not very satisfactory in horizontal projection but becomes satisfactory and clinically useful by application of suitable coefficients, while maintaining the electrode places. The mathematics and the calculations involved are included in this report.

RINZLER

Palmer, J. H.: Complete Heart Block with Rhythmically Recurring Delay and Failure of the Idioventricular Pacemaker. Am. Heart J. **51:** 156 (Jan.), 1956.

A case of complete heart block is described, in which Stokes-Adams seizures resulted from rhythmically recurring slowing and arrest of the ventricular pacemaker. This persisted for several days, during which time it could be suppressed temporarily by epinephrine. The hypothesis is put forward that there is in ectopic rhythms, under certain circumstances, a tendency for the rate to wax and wane. Occasionally this becomes pronounced and may be rhythmically recurrent. It probably is pathologic, and is not dependent on vagus activity. Nonphasic sinus arrhythmia may be an expression of the same tendency in the sinus node. The phenomenon is important clinically in that it is concerned with the beginning and the termination of ectopic tachycardias; during complete heart block it can be responsible for a hitherto undescribed variety of Stokes-Adams attack.

RINZLER

ENDOCRINE EFFECTS ON CIRCULATION

Chalmers, T. M., Fitzgerald, M. G., James, A. H., and Scarborough, H.: Conn's Syndrome with Severe Hypertension. Lancet **1:** 127 (Jan.), 1956.

A 43-year-old housewife is described in whom hypertension (B.P. 225/140) and recurrent paralysis from excessive urinary loss of potassium occurred. There was a low ratio of sodium to potassium in the saliva. Alkalosis was slight or absent. Urinary concentrating power was lost but capacity for acidifying the urine was little impaired.

A tumor was identified in the right kidney by presacral oxygen insufflation and tomography. Removal of the right adrenal gland was followed by correction of the electrolyte abnormality and lowering of the blood pressure.

Estimations of urinary and blood aldosterone levels were within normal limits. Renal biopsy showed vacuolization of the proximal tubules. Isotope dilution and renal biopsy studies showed that the patient's tissues had more sodium and less potassium than normal. Renal clearances of inulin and PAH were low and were further lowered after operation, in a fashion roughly proportional to the drop in pressure. Preoperatively the renal clearance of potassium exceeded that of inulin, in spite of a low serum concentration of potassium (1.9 mEq./L.), and there was a constantly low hydrogen-ion excretion. After operation the potassium-inulin clearance ratio became 0.4 and random samples of urine were acid.

This report supports Conn's suggestion that cases of primary aldosteronism should be sought among hypertensive subjects and among cases of supposed "potassium-losing nephritis."

MCKUSICK

HYPERTENSION

Taquini, A. A., Flesch, S. A., Capris, T. A., and Badano, B. N.: Some Observations on Water and Electrolyte Metabolism in Essential Hypertension. Acta cardiol. **11:** 109 (Fasc. 2), 1956.

Seventeen patients with essential hypertension, 29 to 50 years old, without clinical, laboratory or ophthalmologic evidence of cardiac or renal failure were placed on a strictly controlled diet containing 2.9 mg. of sodium and 3.05 mg. of potassium. Following allowance for a period of adaptation, a number of laboratory tests were performed with the following results. The serum sodium was slightly elevated in 8 cases in whom clinical evidence suggested a more advanced stage of the disease. The serum potassium was elevated in the majority of cases but no clear relationship was found with regard to the stage of the disease or the serum sodium values. Total blood and plasma volumes were normal in all instances. Water tolerance tests revealed earlier and increased excretion of the water load; this was also true of sodium excess, when the latter was added to the water load. No evident modification in handling of water and sodium occurred under the influence of DOCA, in contrast to normal subjects.

These data are compared with results reported by others under experimental and clinical conditions and are discussed in the light of recent advances in the study of renal function in arterial hypertension. Endocrine factors are considered, which may be responsible for alterations in the water and electrolyte metabolism. The results of this study permitted no conclusion regarding the pathogenetic interrelationship between hypertension, renal or hemodynamic alterations, and pituitary-adrenal disorders.

PICK

Fregly, M. J., Yates, F. E., and Landis, E. M.: Serum Sodium Concentration of Hypertensive Rats: Relation to NaCl Intake, Blood Pressure and Age. Proc. Soc. Exper. Biol. & Med. **90:** 695 (Dec.), 1955.

Alterations of sodium metabolism have been studied intensively in both experimental and clinical hypertension. Changes in serum sodium concentration have been reported by others to be variable. Encapsulating both kidneys of young rats (50 to 90 days) in molded latex envelopes produced hypertension and elevated their mean serum sodium concentration. The same procedure in older rats (126 to 165 days) produced similar hypertension but mean serum sodium concentration remained within normal limits. It appears that certain general changes in sodium metabolism occur in association with the experimentally hypertensive state under some conditions. Further studies are needed to explore possible mechanisms by which the 2 may conceivably be linked.

AVIADO

PATHOLOGY

Jacobs, H. D., and Elliott, G, A.: Cardiac Ventricula Aneurysm in South Africa. Acta med. scandinav. Suppl. **306:** 84, 1955. Abstracted, Circulation **14** 630 (Oct.), 1956.

Janett, S. N., Heymann, S., Mundel, B., Paple W. J., Lurie, H. I., Gear, J., Measroch, V., an Kersch, Z.: Myocarditis in the Newborn Infant J. Pediat. **48:** 1 (Jan.), 1956.

An epidemic occurring in newborn infants in maternity home in Johannesburg is described. Te babies between the ages of 5 to 17 days were affected. Six infants died. The illness is a febrile on with some gastroenteritis persisting for a few days and terminated by a sudden fulminating illness suggestive of myocarditis by sign and symptom, ending in circulatory collapse and death. Three of the infants came to autopsy. The outstanding lesion was a focal myocarditis. Virus studies showed that material from brain suspensions of 2 of the autopsied infants produced lesions in brains of suckling-mice resembling those produced by the Coxsackie B virus. A Coxsackie B virus was cultured from the stool of 2 babies who recovered. At the time in Johannesburg an epidemic of Bornholm disease (now known to be caused by Coxsackie virus) was raging within the city. The authors conclude that the Coxsackie B virus can cause an acute infection with associated myocarditis in newborn infants that may terminate fatally.

HARVEY

Matthews, R. J., and Darvill, F. T., Jr.: Fenestrations of the Aortic Valve Cusps as a Cause of Aortic Insufficiency and Spontaneous Aortic Valve Cusp Rupture. Ann. Int. Med. **44:** 993 (May), 1956.

Fenestrations of the aortic valve have been noted infrequently in various autopsy series but the correlation between these fenestrations and symptomatic aortic valvular disease has attracted relatively little attention. In this paper there is reported a case of a Negro man 67 years of age who was admitted with shortness of breath, edema, and other symptoms of congestive failure. The physical examination revealed pulmonary edema and peripheral edema. The heart was enlarged, the enlargement involving the base of the heart and the left ventricle. There was noted a systolic apical murmur and a diastolic aortic murmur of higher intensity. Ultimately, the murmur in the aortic area became louder and was transmitted down the sternum toward the left and was best heard in the fourth interspace. Duroziez' sign was positive, and th

blood pressure was 200/70 mm. During the hospitalization of the patient, a more intense and musical diastolic aortic murmur appeared. After a prolonged course of intractable heart failure, the patient died. The autopsy demonstrated many fenestrations of the aortic and pulmonary valves. The right anterior leaflet of the aortic valve was ruptured across the area of 1 fenestration. There was also noted a fusion of the aortic valve commissures, presumably as the result of a previous rheumatic valvular infection. Sections of the aortic valve cusps revealed a mucinous degeneration of the valve substance. It is the conclusion of the authors that at the fusion of the aortic valves caused an abnormal degree of friction of this valve and that in the presence of such friction and degeneration of the valve substance, eventually a rupture through 1 of the congenital fenestrations occurred. It is therefore suggested that fenestrations of the semilunar valves be considered in any differential diagnosis of aortic insufficiency, especially when the common causes of aortic insufficiency, such as syphilis and rheumatic fever do not seem to be the obvious ones.

WENDKOS

PATHOLOGIC PHYSIOLOGY

Smith, G., and Smith, A. N.: The Role of Serotonin in Experimental Pulmonary Embolism. Surg., Gynec. & Obst. **101:** 691 (Dec.), 1955.

The authors call attention to the finding that often the general effects of pulmonary embolism far exceed those that might be expected from the size of the embolus. To account for the discrepancy between the symptoms observed and the size of the embolus and the area of the lung bed affected, depressor reflexes elicited from the lung vessels themselves have been implicated as contributing to the severity of the clinical picture. The authors offered another possibility, that serotonin might be released from the blood clot and the infarcted area of lung and that it might be responsible for some of the findings. It is generally accepted that this substance causes constriction of the coronary vessels, excitation of the coronary chemoreflex, stimulation of carotid sinus, baroreceptors and chemoreceptors, and direct constriction of the great veins, trachea and bronchi.

To subject their theory to experimental proof, the authors studied a series of cats in whom mechanical embolization of the pulmonary bed had been produced using potato starch granules. The amount of serotonin was determined in the plasma and blood extracts.

It was found that serotonin was released into the serum of clotting blood and was present in the blood clot itself. It was noted that this substance caused a rise in the pulmonary arterial pressure. When injected so as to by-pass the lung bed, the vascular effects were minimized.

The authors concluded that while many active agents are released from clotting blood, the signs and symptoms of experimental pulmonary embolism may depend on the liberation to some considerable extent of serotonin from both the blood clot and the infarcted area of lung.

ABRAMSON

Daly, M. de B., and Schweitzer, A.: The Effects of Stimulation of the Carotid Sinus Baroreceptors upon the Pulmonary Arterial Blood Pressure in the Dog. J. Physiol. **131:** 220 (Jan.), 1956.

Compared with the vast literature on the effects of sinoaortic reflexes upon the systemic circulation, few observations have been made on their corresponding effects upon the pulmonary circulation. Bilateral occlusion of the common carotid arteries causes a reflex rise in pulmonary arterial pressure, whereas stimulation of the carotid sinus nerve causes a fall. Evidence is presented that suggests the effects on pulmonary arterial pressure are, at least in part, secondary to hemodynamic events occurring in the systemic circulation and to the cardiac affects.

AVIADO

Montagnani, C. A., and v. Elzenbaum, H.: Experimental Investigations on the Mechanism of Formation of Ascites. Arch. "de Vecchi" anat. pat. **23:** 665 (Aug.), 1955.

By introducing into the inferior vena cava, at the level of the openings of the hepatic veins, an interstitial glass tube of diameter only slightly smaller than the diameter of the vein itself, marked resistance to flow in the hepatic veins and passive congestion of the liver are produced without significantly increasing the venous pressure in the inferior vena cava and the other veins opening in it. Nine dogs have been successfully operated upon. Three weeks to 2 months after the operation, ascites developed and reaccumulated rapidly after tapping. Venous pressure in the inferior vena cava and in the vena porta was not significantly increased. Bromosulphalein elimination has been found within normal limits in these dogs. At postmortem examination, 15 to 45 days after the appearance of ascites, the liver was much enlarged and congested, in some cases with initial "nutmeg" changes. Histologically, the intrahepatic sinusoids were grossly enlarged and separated from the hepatic cells by enlarged Disse's spaces filled with a granular substance, probably clotted protein; the hepatic cells are essentially well preserved. From their observations the authors conclude that hypertension of the intrahepatic sinusoids is an essential factor in the

mechanism of increased hepatic lymphatic flow and ascites formation.

CALABRESI

Mottu, T.: The Mechanical Force of the Heart and Cardiovascular Efficiency: Effects of Exercise and Digitalis. Arch. mal. coeur **49:** 53 (Jan.), 1956.

The "mechanical force of the heart" is defined as the cardiac work per unit of time, the "mechanical cardiovascular efficiency" as the work done by the peripheral circulation divided by the work of the cardiac systole, and "efficiency of force" as the "force" of the peripheral circulation divided by the "systolic force" of the heart. In 15 patients treated with lanatoside C or Strophosid, the cardiac work and "force" increased, but the "cardiovascular efficiency" decreased. In 7 cases exercise caused an increase of cardiac work and "force" but an unchanged "cardiovascular efficiency" and an increased "efficiency of force." This theoretic conclusion that digitalis decreases the economy of cardiac work does not permit any practical conclusions.

LEPESCHKIN

Gerard, R., and Benyamine, R.: Classification of Capillary Pulmonary Pressure Pulse in Mitral Lesions. Arch. mal. coeur **49:** 31 (Jan.), 1956.

In 45 cases of mitral stenosis with sinus rhythm, the first type of pulse curves showed an A wave exceeding the V wave in amplitude, a late diastolic pressure of 10 and a mean pulmonary pressure of 24 mm. Hg. The second type showed *a* and *v* waves of equal magnitude with pressures of 23 and 40, while the third type had predominant *v* waves and pressures of 28 and 53 mm. Hg respectively. The second and third types corresponded to tight mitral stenoses found during valvulotomy. In mitral insufficiency (16 cases) the *v* wave also predominated, but showed an early summit and steep descent, and its peak pressure was more than twice as great as the late diastolic pressure. In 20 mitral stenosis cases with atrial fibrillation, the pulse curve began with a negative depression 0.1 sec. after QRS, which corresponded to the beginning of ventricular ejection. This depression was followed by a *c* wave that showed an apex 0.14 to 0.16 sec. after QRS and an amplitude inversely proportional to the length of the preceding diastole; this wave was attributed to ballooning of the mitral valve into the left atrium during ventricular contraction.

LEPESCHKIN

VASCULAR DISEASE

Creed, D. L., Baird, W. F., and Fisher, E. R.: The Severity of Aortic Arteriosclerosis in Certain Diseases: A Necropsy Study. Am. J. M. Sc. **230:** 385 (Oct.), 1955.

An evaluation of the severity of aortic arteriosclerosis occurring in 1,223 necropsies performed on males at a Veterans Administration Hospital over a 7-year period is reported in order to determine the influence of a variety of diseases upon the process. The sclerotic process was found to be more severe in patients succumbing to hypertension and bronchogenic carcinoma than in control patients. The aorta of patients with malignant lymphoma or leukemia revealed a statistically significant decreased severity of arteriosclerosis in the range of 51 to 60 years. A similar decrease in sclerosis was noted in patients with Laennec's cirrhosis. The mechanism of increased arteriosclerosis in patients with bronchogenic carcinoma is unexplained. The decreased severity in cirrhosis may be related to the clearing action of estrogen upon serum lipoproteins; failure of estrogen inactivation in chronic liver disease is well-known. In addition, the presence of jaundice is associated with an increase in serum phospholipids that aids in stabilization of serum lipid emulsions. The hepatic involvement noted in patients with malignant lymphoma and leukemia may account for the decreased severity of arteriosclerosis on the same basis as in cirrhosis. The prolonged poor nutritional status which many of these patients exhibit is associated with a reduced severity of the sclerotic process.

SHUMAN

Palmer, E. D., and Brick, I. B.: Varices of the Distal Esophagus in the Apparent Absence of Portal and of Superior Vena Caval Hypertension. Am. J. M. Sc. **230:** 515 (Nov.), 1955.

Esophageal varices are classified by the authors in 4 categories: (1) the usual type of distal or mid-esophageal varices secondary to venous hypertension; (2) a rare form of primary varices limited to the uppermost part of the esophagus arising from the posterior hypopharyngeal plexus; (3) varices with idiopathic portal hypertension; and (4) idiopathic varices in the distal esophagus without portal or superior caval hypertension. There were 13 patients with the last type of varices in 350 patients with esophageal varices. Portal pressure was measured in 4 of this group, signs of increased portal or supradiaphragmatic venous pressures were absent in all of them. Liver biopsies and hepatic function tests were normal. Esophagoscopy revealed that the varices were largest at the esophagastric junction and became smaller in their cephalad extensions. The diagnosis is difficult to establish because, in the absence of venous pressure measurements within the varices, it is a diagnosis of exclusion. Esophageal varices in the absence of venous hypertension may be responsible for hemorrhage; however, in the present group, the bleeding was not severe. It is probable that esophagitis is the responsible factor in such bleeding.

SHUMAN

Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in Cerebrovascular Disease. V. The Use of Anticoagulant Drugs in the Treatment of Intermittent Insufficiency of the Internal Carotid Arterial System. Proc. Staff Meet., Mayo Clin. **30:** 578 (Nov.), 1955.

A number of procedures, including the administration of anticoagulant drugs, have been used in the treatment of thrombosis of the internal carotid artery. None of these treatments has been effective in changing the cerebral infarction ordinarily associated with such a thrombosis. Greater emphasis should be placed on trying to anticipate catastrophe. In the past, primary interest has been concentrated where definite and often serious cerebral infarction has already occurred, with all too little favorable effect by any type of treatment. Careful inspection of historical and physical data may well lead to the ability to diagnose a potential infarction and even, in certain instances, to prevent it. With this concept in mind, a diagnosis of intermittent insufficiency of the internal carotid artery has been established in 7 instances. The patients were treated with anticoagulant drugs and the characteristic attacks ceased. The number of these patients who would subsequently have suffered thrombosis of the artery is not known. The correct duration of such treatment is not known, although long-term anticoagulant therapy is advised. The pathogenesis of the disorder is discussed.

SIMON

Ring, A., and Bakke, J. R.: Chronic Massive Pulmonary Artery Thrombosis. Ann. Int. Med. **43:** 781 (Oct.), 1955.

A total of 11,511 consecutive autopsies from the Queens Hospital Center, Jamaica, N. Y., was reviewed. Twenty-one cases of chronic massive pulmonary artery thrombosis (an incidence of 0.18 per cent) were found. The age incidence varied from an infant of 15 months to a female of 89 years. Both the mean and median ages were 59 years. Both right and left main pulmonary arteries were involved in 8 cases, the right main pulmonary artery in 9, and the left in 4. Six of the cases were secondary to previous pulmonary embolization. In the remaining 15 cases the authors could not be certain, but several of these were probably autochthonous. Fifteen of the cases were associated with chronic pulmonary disease. The clinical picture was usually masked by the underlying chronic pulmonary or cardiac disease. However, the outstanding symptom was dyspnea out of proportion to the underlying disease and usually refractory to all treatment. A history or clinical evidence of preceding pulmonary embolization may also be helpful in some instances. When pulmonary thrombosis is suspected, x-ray of the chest, fluoroscopy, and angiocardiography may provide additional confirmatory evidence. The terminal clinical picture in many instances was that of a failing cor pulmonale. As this syndrome receives more recognition, the clinical diagnosis should be made with greater frequency in the future. When diagnosed, a prolonged trial of anticoagulants is justified in view of the usually dire prognosis.

WENDKOS

Zbar, M. J.: Ischemic Necrosis of the Legs as a Complication of Coarctation of the Aorta. Ann. Int. Med. **43:** 1099 (Nov.), 1955.

A case is presented of coarctation of the thoracic aorta in a 43-year-old Negro woman, associated with bilateral ischemic necrosis of the lower extremities. The aorta also exhibited marked subintimal scarring that was secondary to syphilitis aortitis and that augmented the obstructive effect of the coarctation. Since individuals with coarctation meet demands for increased blood flow poorly, such a "functional difference" might well have been operative in this case. Severe coarctation of the aorta and prolonged trauma to the legs with inadequate collateral circulation might well have initiated the development and facilitated the progression of the ischemic changes when additional demands such as infection and congestive heart failure were superimposed. The abnormalities of the aorta in this case must have been congenital. It is conceivable that the lesion might have been acquired, but its location and general configuration are certainly typical of the congenital deformity. The indentation of the aortic wall at the site of the coarctation was not so apparent as that usually described, and the channel through the obstruction was in a posterolateral situation rather than in the region of insertion of the ligamentum arteriosum. Otherwise, the wedge-shaped structure causing the stenosis was generally similar to those previously described. The medial elastica, however, did not participate in the formation of the wedge, in contrast to the findings in all cases of coarctation of the aorta previously reported. However, the intimal thickening at the zone of aortic narrowing, said to be present in specimens from adults and adolescents, was strikingly shown in this case.

WENDKOS

Brando, M.: Thrombosis of Internal Carotid Artery in Childhood after Injuries in Region of Soft Palate. Brit. M. J. **1:** 665 (Mar. 24), 1956.

The author describes 3 children who sustained injury to the soft palate area because of falling down with sharp objects in the mouth—a metal rod, a pencil, a small garden stake. The accident was followed by contralateral hemiplegia and other neurologic manifestations. Early use of anticoagulants is probably indicated and possibly sympathetic block.

MCKUSICK

Konhaus, C. H., and Kunkel, P. A. Jr.: Aneurysm of a Pulmonary Artery: Report of a Case in which

Treatment was Surgical. Ann. Surg. **142:** 997 (Dec.), 1955.

The authors described a case of aneurysm of a branch of the right pulmonary artery supplying the lower lobe of the right lung, which was treated by lobectomy. Despite extensive laboratory and physical examinations, the diagnosis was not established until the lesion was examined at operation. The aneurysm was believed to be congenital in origin.

ABRAMSON

Moyes, P. D., Wakim, K. G., Sayre, G. P., and Millikan, C. H.: Studies in Cerebrovascular Disease. VI. Experimental Cerebral Infarction: A Study of Different Technics. Proc. Staff Meet., Mayo Clin. **30:** 620 (Dec.), 1955.

Attempts to produce cerebral infarction in dogs were made by the injection of 5 combinations of materials into the internal carotid artery in the neck. The use of combinations of topical thrombin and sodium morrhuate solutions alone or mixed with blood proved unsatisfactory. When infarcts were present, death of the animal occurred within 24 to 36 hours in the majority of the cases. The injection of 48-hour-old homologous blood clot alone appeared to be promising as a satisfactory method in that in a reasonable number of animals infarcts occurred and animals survived an adequate length of time to permit clinical and pathologic study.

SIMON

Kleh, J., and Fazekas, J. F.: Effects of Hypotensive Agents on Subjects with Cerebral Vascular Insufficiency. J. Am. Geriatrics Soc. **4:** 18 (Jan.), 1956.

A comparative study of the effects of reserpine, hexamethonium, or the combination of reserpine and hydralazine on cerebral hemodynamics and metabolism was made on 5 subjects with hypertensive cerebral vascular disease. Reserpine alone in moderately large doses caused only a slight reduction of blood pressure and no change in cerebral hemodynamics and metabolism. The subcutaneous administration of hexamethonium was associated with a significant reduction of pressure and of cerebral vascular resistance but no change in either cerebral blood flow or metabolism. Frequent episodes of cerebral vascular insufficiency were noted and seemed to be related to acute reductions in pressure. The combination of hydralazine and reserpine induced a significant reduction of pressure and cerebral vascular resistance but no change in the rate of cerebral blood flow or metabolism. The authors recommend the combination of hydralazine and reserpine as the safest and most effective method for the control of hypertension of patients with cerebral vascular disease.

RINZLER

Hill, N. C., Millikan, C. H., Wakim, K. G., and Sayre, G. P.: Studies in Cerebrovascular Disease. VII. Experimental Production of Cerebral Infarction by Intracarotid Injection of Homologous Blood Clot. Preliminary Report. Proc. Staff Meet., Mayo Clin. **30:** 625 (Dec.), 1955.

The intracarotid injection of homologous clot in the dog is a simple procedure that produces a high rate of infarction (80 per cent) with a low mortality rate (16 per cent). The infarcts produced resemble, in some of their clinical and pathologic features, infarcts resulting from interruption of cerebral circulation in man. A standardized system of estimating the gross extent and appearance of the infarcts produced is described. In general, clinical signs could be correlated with the site and size of infarction produced. In the group of animals that survived, there was no correlation between the degree of hemorrhagic infarction and the severity of clinical signs.

SIMON

Reedy, W. J., Koszewski, B., and Murphy, P.: Evaluation of Aortic Occlusion by Aortography. Ann. Int. Med. **44:** 283 (Feb.), 1956.

Aortography, or the contrast visualization of the aorta and its branches, has played an important part in recent advances in diagnosis. Although abdominal aortography is not new, only within the past decade has it been established as more than a medical adventure. Included in this report are illustrative examples of arteriosclerotic abdominal aneurysm, chronic aorto-iliac obstruction, segmental narrowing or thrombosis of the larger arterial trunks of the lower extremities, which are demonstrable by this technic.

WENDKOS

Sokolow, J., Kaplan, L. I., and Rusk, H. A.: The Rehabilitation of Hemiplegics with Auricular Fibrillation. Arch. Int. Med. **97:** 73 (Jan.), 1956.

In an effort to improve their ability to carry out the various physical activities of a program of rehabilitation, conversion of atrial fibrillation to regular sinus rhythm was attempted in 4 hemiplegic patients with a history of 1 or more embolizations. In 3 of the 4 cases the heart rate was successfully converted to regular rhythm with an improvement in the patients' clinical efficiency and in their circulatory hemodynamics.

BERNSTEIN

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PRESENT GOLD HEART, LASKER AND BLAKESLEE AWARDS

Two Gold Heart Awards, the Albert Lasker Award and seven Howard W. Blakeslee Awards were among the honors conferred by the American Heart Association at its Annual Meeting and Scientific Sessions in Cincinnati, October 26 to November 2.

Gold Hearts

The Gold Heart Awards for outstanding contributions to cardiovascular medicine and to the Heart program were given to Arlie R. Barnes, M.D., Rochester, Minn., and to General Mark W. Clark, Charleston, S.C. Presentation was made at the AHA Annual Dinner, Sunday, October 28.

In honoring Dr. Barnes, the Association paid tribute to a medical pioneer whose many distinguished contributions to cardiovascular medicine include original studies on electrocardiographic changes produced by coronary disease and by pericarditis, and on the efficacy of ACTH and cortisone in acute rheumatic fever therapy. Dr. Barnes is currently Professor of Medicine at the Graduate School of the University of Minnesota and is a former Chairman of the Board of Governors of the Mayo Clinic. He served for many years as an officer and director of the American Heart Association and was President of the Association in 1947 and 1948.

General Clark, whose distinguished military career included service as United States Commander-in-Chief in the Far East, is now President of The Citadel, the military college of South Carolina at Charleston. He has been National Campaign Chairman of the Heart Fund during the past 3 years.

Dr. L. N. Katz Honored

The Albert Lasker Award of the American Heart Association, which pays tribute to distinguished achievements in cardiovascular research, was presented at the Scientific Sessions on October 27 to Louis N. Katz, M.D. Dr. Katz, former President of the American Heart Association and current President of the Chicago Heart Association, is Director of the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago.

In presenting the Lasker Award to Dr. Katz, the association paid tribute to his experimental studies in atherogenesis and to his many other contributions in the fields of electrocardiography and teaching. The Lasker Award consists of a statuette of the Winged Victory of Samothrace and an honorarium of $1,000. The award is given annually through the American Heart Association by the Albert and Mary Lasker Foundation.

Blakeslee Awards

Seven winners representing newspapers, magazines, radio and television were presented with Howard W. Blakeslee Awards for outstanding reporting in the cardiovascular field at the Annual Dinner. In addition a special Blakeslee Award was made to Paul D. White, M.D., for "creating better public understanding of heart disease through his press conferences, published articles, and radio and television appearances during the illness and recovery of President Eisenhower."

Recipients of the regular Blakeslee Awards, each of which included an honorarium of $500, were:

Frank Carey, science reporter, Associated Press, Washington, D.C., for year-round coverage.

Nate Haseltine, science writer, Washington Post and Times Herald, for his series on pediatric cardiology and cardiovascular surgery, "Within a Child's Heart."

Robert P. Goldman, Science Editor and Assistant Managing Editor, Parade Magazine, for a series presenting new developments in cardiovascular research and treatment.

Science Department, Life Magazine, for a pictorial article on coronary thrombosis.

Howard Whitman, medical commentator on the National Broadcasting Company's TV "Home Show," for a series of four programs entitled "Your Heart" filmed at medical and research centers.

George Voutsas, producer-director, and *Earl Hamner*, writer, for the NBC radio broadcast, "Courage to Live," a documentary presentation on a patient who faces the decision to undergo heart surgery.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH MEETS NOVEMBER 30

Studies on renal function and pathology, on relationships between adrenal hormones and hypertension, on emotional factors as they relate to coronary occlusion and on the latest advances in the fields of hypertension and atherosclerosis will be featured on the program of the Annual Meeting of the Association's Council for High Blood Pressure Research. The meeting is scheduled for the Hotel Cleveland, Cleveland, on Friday and Saturday, November 30 and December 1.

The program will also include an address by Paul D. White, M.D., on Friday evening. Participation in the meeting is by invitation.

The *Proceedings* of last year's Annual Meeting of the Council for High Blood Pressure Research are available from the Association. Cost of the 160-page volume is $4.50 per copy. For those who wish a complete set including *Proceedings* of the 1952, 1953, 1954, and 1955 meetings of the Council, these may be obtained at a special combined price of $7.50. Orders should be addressed to the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N.Y.

NAS-NRC RESEARCH FELLOWSHIP APPLICATIONS BEING ACCEPTED

Applications for postdoctoral research fellowships for 1957–58 will be accepted by the Division of Medical Sciences of the National Academy of Sciences-National Research Council until December 1, 1956.

Three groups of fellowships are involved. They are the National Research Fellowships in the Medical Sciences (supported by the Rockefeller Foundation), the Donner Fellowships for Medical Research and the Markle Fellowships in the Medical Sciences. All are designed to offer research experience to those who intend to make careers in investigation and academic medicine. Fellows are expected to devote their full time to fundamental research.

Full information and application forms may be obtained from the Division of Medical Sciences, Room 310, National Academy of Sciences-National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D.C.

SCHEDULE HOUSTON ECG COURSE DECEMBER 3-7

A course in practical electrocardiography under the direction of Dr. Demetrio Sodi-Pallares, Chief of the Department of Electrocardiography of the National Institute of Cardiology, Mexico City, will be presented in Houston, December 3–7. The course will be sponsored jointly by the university of Texas Postgraduate School of Medicine and Baylor University College of Medicine.

Dr. Sodi-Pallares' course will be given during the evenings. The daytime will be devoted to individual instruction in ECG reading by faculty members of the sponsoring institutions and panel discussions on subjects of special interest to electrocardiologists for more advanced students. Further information may be obtained from the University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25, Tex.

NEW ENGLAND CARDIOVASCULAR SOCIETY PROGRAMS PLANNED

The New England Cardiovascular Society has launched its 1956–57 scientific program with five meetings at the Morse Auditorium, Museum of Science, Boston, on November 5. Additional programs, all scheduled for the Morse Auditorium, will be held on the following dates: January 14, 1957; February 11; March 11; and May 13 (The Henry Jackson Lecture).

Hospitals and medical centers participating in the programs include the Peter Bent Bri-

ham Hospital; Beth Israel Hospital; Massachusetts Memorial Hospitals; Children's Medical Center; Boston City Hospital and the Massachusetts General Hospital.

Additional information may be obtained from Alexander S. Nadas, M.D., Secretary, The New England Cardiovascular Society, c/o The Massachusetts Heart Association, 650 Beacon Street, Boston 15, Mass.

PUBLISH OUTSTANDING PAPERS FROM WORLD CARDIOLOGY CONGRESS

Five volumes containing outstanding papers and panels presented at the Second World Congress of Cardiology are being published through an arrangement with the Association. The volumes bear the title "World Trends in Cardiology." One volume is devoted to each of the following subjects:

Cardiovascular Epidemiology; Cardiovascular Surgery; Blood Volume and Contractile Protein in Heart Muscle; Cardiovascular Diagnosis and Therapy; Instrumental Methods in Cardiac Diagnosis.

Full information on the series and on the individual volumes may be obtained directly from the publisher, Paul B. Hoeber, Inc., Medical Book Department, Harper and Brothers, 49 E. 33 St., New York 16, N.Y.

RELEASE AHA FILM ON BASIC RESEARCH

"The Secrets of the Heart," the Association's motion picture on basic research, is now being distributed by state and local Heart Associations throughout the country.

The sound film is a dramatic presentation in which the audience has an opportunity to view investigations being conducted at several leading research centers. Emphasis is on fundamental studies and their relationship to cardiovascular medicine and surgery. Irvine H. Page, M.D., President of the Association, acts as guide and commentator. The film was produced for the Association by MPO Productions Inc. and was written and directed by George C. Sweeney. This is the team which made the earlier Association film on rheumatic fever, "The Valiant Heart."

Running time of the 16 mm. sound film is 29 min. Information may be obtained from the American Heart Association, 44 East 23 Street, New York 10, N. Y. or from your state or local Heart Association.

FOUR CLINICAL RESEARCH AREA MEETINGS SCHEDULED

Four 1956–57 section meetings have been scheduled by the American Federation for Clinical Research during the coming months. The schedule of the area scientific sessions is as follows:

Midwestern—Thorne Hall, Northwestern University Medical Campus, Chicago, Thursday, November 8.

Eastern—Hurd Hall, The Johns Hopkins Hospital, Baltimore, Friday, December 7; and Gordon Wilson Hall, University of Maryland Hospital, Baltimore, Saturday, December 8.

Southern—Jung Hotel, New Orleans, Friday, January 25.

Western—Golden Bough Theatre, Carmel, Calif., Wednesday and Thursday, January 30–31.

MEETINGS CALENDAR

Nov. 11–12: American Society for the Study of Arteriosclerosis, Chicago. O. J. Pollak, M.D., P.O. Box 228, Dover, Del.

Nov. 12–16: American Public Health Assn., Atlantic City, N.J. R. M. Atwater, American Public Health Assn., 1790 Broadway, New York 19, N.Y.

Nov. 12–18: American School Health Assn., Atlantic City, N.J. A. O. DeWeese, 515 E. Main St., Kent, Ohio.

Nov. 17–19: American Academy for Cerebral Palsy, Chicago. Robert A. Knight, 869 Madison Ave., Memphis 3, Tenn.

Nov. 27–30: American Medical Assn. Clinical Meeting, Seattle. George F. Lull, M.D., 535 N. Dearborn St., Chicago 10, Ill.

Nov. 30–Dec. 1: Council for High Blood Pressure Research of the American Heart Assn., Cleveland. By invitation.

Dec. 2–7: Radiological Society of North America, Chicago. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y.

Dec. 7–8: Association for Research in Nervous and Mental Disorders, New York. Rollo J. Masselink, 700 W. 168 St., New York 32, N.Y.

Jan. 16–18: Conference on Cerebral Vascular Diseases, Princeton, N.J. Irving S. Wright, M.D., Cornell Medical Center, 1300 York Ave., New York 21, N.Y. By invitation.

Jan. 16–19: Neurosurgical Society of America, Palm Springs, Calif. Frank P. Smith, 260 Crittenden Blvd., Rochester 20, N.Y.

Feb. 4–6: American Academy of Allergy, Los Angeles. Francis C. Lowell, 65 E. Newton St., Boston.

Feb. 8–9: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Dr., Chicago 6, Ill.

ABROAD

Nov. 11–17: Inter-American Congress of Cardiology, Havana. Dr. Ignacio Chavez, Calzada de la Piedad Num. 300, Mexico City.

Dec. 1–15: Bahamas Medical Conference, Nassau, B.W.I. B. L. Frank, M.D., 550 Fifth Ave., New York 36, N.Y.

Jan. 3–6: 14th International Congress of Union Against Tuberculosis, New Delhi. Union Against Tuberculosis, 66 Blvd. St. Michel, Paris 6°.

Feb. 24–28: Biennial International Scientific Congress, International College of Surgeons, Mexico City. Dr. Max Thorek, Intl. College of Surgeons, 850 Irving Park Rd., Chicago 13, Ill.

ABSTRACTS OF PAPERS

of the

29th SCIENTIFIC SESSIONS

of the AMERICAN HEART ASSOCIATION

October 26–29, 1956

Music Hall

Cincinnati, Ohio

The Program of these Sessions was published in the October issue of Circulation.

ABSTRACTS OF PAPERS

LEWIS A. CONNER MEMORIAL LECTURE

Functional Pathology of the Pulmonary Vascular Tree in Congenital Cardiac Disease

Jesse E. Edwards, Rochester, Minn.

Response of the pulmonary vascular tree may be an integral part of the dynamics in certain cardiovascular malformations. The role of this segment of the circulatory system is most significant when there is a free communication between the ventricles or great arteries in the absence of pulmonary stenosis, obstruction to pulmonary venous flow, or coexistence of the 2 foregoing circumstances.

In the presence of a free communication between the ventricles or great arteries, and of pulmonary stenosis also, the structure of the pulmonary vascular bed is essentially normal and its functional response is evidently normal.

In the absence of pulmonary stenosis, a free communication between the ventricles or great arteries is associated with thick muscular medial coats in the small pulmonary arteries. This condition correlates with the functional feature of a high resistance to pulmonary flow. The high resistance is a governing factor in the direction and magnitude of shunts across the abnormal communication. Pulmonary hypertension is an associated condition.

In examples of obstruction to pulmonary venous flow, there are likewise hypertrophy of the medial coats of the small pulmonary arteries and a high "arteriolar" resistance to flow. This high resistance is a governing factor in the amount of blood reaching the pulmonary capillaries and hence a factor in the degree of pulmonary capillary pressure. Usually the pulmonary capillary pressure is high but not high enough to produce pulmonary edema. In these cases pulmonary arterial hypertension also exists.

In the presence of a free communication between the ventricles or great arteries, and also of pulmonary venous obstruction, the structural changes and governing factors of the pulmonary vascular bed are like those in each of the foregoing circumstances.

Simple muscular medial thickening seems to be associated with a readily changeable response on the part of the pulmonary vascular bed. In time the associated pulmonary hypertension may be complicated by intimal lesions that cause anatomic occlusion of lumens. This condition is followed not only by an intensification of the high degree of pulmonary vascular resistance but also by loss in the flexibility of response.

GEORGE E. BROWN MEMORIAL LECTURE

Oxygen Tension of Tissues in Vivo

Hugh Montgomery, Philadelphia, Pa.

Attempts at measurement of oxygen in tissues have never been wholly satisfactory, yet these attempts, like those of measurement of oxygen in blood and other body fluids, go back many years. It is safe to say that it is as important to measure the concentration or tension of oxygen in tissues as it is in blood and other fluids that can be drawn from the body. The early investigators were aware of the need to know how much oxygen exists in this or that tissue, and how it changes with other physiologic changes. However, to date, the methods of measuring oxygen tension in tissues have, in general, been less satisfactory than those for blood and the body fluids.

The amperemetric technic, growing out of polarographic studies, is beginning to contribute some answers to the questions regarding the oxygen tension of tissues in situ. The method has the advantage that a fine-pointed electrode can be inserted into the tissue and that the flow of electric current is proportional to the rate of delivery of oxygen from the tissue to the electrode.

Prior to the use of the oxygen electrode there was a rather static concept of the oxygen tension of tissues. As a result of the polarographic technic the concept of much more dynamic alterations in oxygen tension of tissues is arising.

Most of the studies of our laboratory are concerned with physiologic and pathologic changes in oxygen tension in the skin and skeletal muscle in man. The relationship of changing oxygen tension of tissue to changing circulation, and oxygen utilization, is stressed.

Some of the history of the earlier attempts at measuring oxygen in body fluids and tissues is reviewed. Some of the important recent contributions of other investigators, using the polarographic technic in various tissues, are discussed.

Abstracts are printed alphabetically according to the senior authors.

(*) *Research Fellow, American Heart Association, 1955–1956.*
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Clinical Value of Left Heart Catheterization in the Evaluation of Aortic and Mitral Stenosis

Walter H. Abelmann,† Ernest W. Hancock, Rhett P. Walker, and George W. B. Starkey, Boston, Mass.

By means of left heart catheterization the degree of mitral and aortic stenosis can be satisfactorily measured, provided pressures on both sides of the valve and valve flow are obtained simultaneously. Thirty such procedures have been performed without major complication.

The striking clinical value of left heart catheterization in the evaluation of patients for aortic or mitral surgery will be illustrated by selected cases.

In aortic stenosis, demonstration of a significant systolic pressure gradient across the aortic valve has become the prerequisite for aortic valvulotomy, and left heart catheterization has replaced the often misleading determination of pressures at thoracotomy. All the clinical features of aortic stenosis may be present without demonstrable pressure gradient in patients with coronary and myocardial disease with coincidental, functionally unimportant changes in the aortic valve. On the other hand, severe aortic stenosis has been demonstrated in the absence of significant symptoms. One patient with clinically pure aortic stenosis had physiologically pure mitral stenosis. Clinical evidence of multi-valvular disease was often associated with a single valvular lesion of physiologic significance.

In mitral stenosis, patients with atypical symptoms and those suspected of significant myocardial disease can be screened for operation more effectively by left heart catheterization than by other methods.

Presence of significant mitral insufficiency is usually detected by the left atrial pressure tracing, but its quantification awaits improved methods of measuring regurgitant blood flow. The increased forward mitral flow in combined mitral stenosis and regurgitation may result in a large mitral diastolic gradient and a gross over-estimate of mitral stenosis by conventional valve formulas.

It is concluded that left heart catheterization contributes greatly to the evaluation of aortic and mitral lesions and has significantly reduced the need for exploratory thoracotomy in a group of patients whose operative risk in the absence of operative benefit is high.

Display of Spatial Vectorcardiographic Data on a Linear Time Scale

J. A. Abildskov, Syracuse, N. Y., and William E. Ingerson, El Paso, Tex.

Vectorcardiograms have certain advantages over electrocardiograms but have a serious limitation in the imperfect indication of time. Their desirabl features can be retained and an adequate representa tion of time achieved by recording simultaneou traces of vector magnitude and orientation wit time. A computer permitting this display has bee constructed and 100 records for preliminary clinica study obtained.

In effect the computer changes the coordinat system in which electric activity is viewed fro rectangular to spherical coordinates. The computa tion is carried out in 1 plane by modulating 2 orthog onal carriers with the heart signal projected on axes. The resultant obtained by linear additio after suppression of carriers is amplitude detecte to yield vector magnitude in the plane. Extensio of these principles to another plane permits spatia magnitude to be obtained. Vector direction is ob tained by detecting the phase difference of resultant signal in each plane and unmodulated reference carriers.

Study of the records has shown that the clinically important information in the electrocardiogram was easily accessible in the new records. In addition, information which could not be readily obtained from the conventional electrocardiogram or vectorcardiogram was made evident. Variations of vector magnitude indicated by notches on the magnitude curves were not apparent from the electrocardiogram or vectorcardiogram. The variable orientation of QRS vectors was reflected by quantitative details of the orientation traces but those showing frontal plane orientation could be categorized into 3 groups and all curves of anteroposterior orientation were qualitatively similar. Many measurements and analyses such as areas enclosed by specific portions of the magnitude curves and kurtosis and skewness of these portions were applicable to the new curves and yielded information not readily obtainable from electrocardiograms or vectorcardiograms. Further studies are necessary to define areas of clinical usefulness of additional information made available by the new display.

Physiologic Studies on the Cardiovascular Status of Normal Newborn Infants With Special Reference to the Ductus Arteriosus

Forrest H. Adams, Los Angeles, Calif., and John Lind, Stockholm, Sweden.

Available information regarding the functional status of the normal newborn human infant's cardiovascular system is meager and, furthermore, much of this has been gained only by indirect means. Necessary to an understanding of the significance of the altered hemodynamics in diseases of this age group, is prior knowledge of the *normal* state and the direction of change with age.

These studies to be reported were undertaken to a certain more accurately the physiologic status of t e heart and great vessels of the normal newborn i fant, with particular emphasis on the changes in l essures and shunts with advancing age.

Physiologic studies including cardiac catheteriza- t on, electrocardiography, and heart volume de- t rminations have been performed on 8 newborn i fants with a normal cardiovascular status, ranging i age from 7 hours to 14 days. The 2 most interesting r sults of these studies were the finding of right v ntricular and pulmonary hypertension of moderate d gree, and a significantly large left-to-right shunt o blood through the ductus arteriosus beyond the t ird day of life.

Significance of Pulmonary Vascular Pathology in Ventricular Septal Defect as Determined by Lung Biopsy

Paul Adams, Russell V. Lucas, Donald K. Ferguson, and C. Walton Lillehei, Minneapolis, Minn.

Fifty patients undergoing intracardiac surgery for ventricular septal defect have had lung biopsies at the time of surgery. Lung sections on autopsied cases have also been reviewed, many of which cases also had lung biopsies just prior to death. Elastic tissue staining was used on all sections. Biopsy and autopsy sections were graded for severity of pulmonary arteriolar change according to whether they were (1) normal, (2) grade I (medial hypertrophy plus no more than 2 vessels with intimal proliferation per cm.^{2}), (3) grade II (3 to 5 vessels with intimal proliferation per cm.^{2}), or (4) grade III (5 or more vessels with intimal proliferation per cm.^{2}). The gradings were done with no knowledge of the patient's name or subsequent course in the hospital.

Twelve of the sections showed grade III pathologic changes and none of these patients survived surgery. Incidentally, none of these patients showed systemic desaturation. Sixteen of the sections were graded as normal and all of these patients survived surgery. Sections graded as 1 or 2 comprised the remaining 22 patients. One half of these patients failed to survive and were equally distributed between the 2 groups.

Little correlation was shown between pulmonary pathology and direct physiologic measurements of pressure, and calculated measurements of flow and resistance. However, when pulmonary artery systolic pressure was expressed as a percentage of systemic systolic pressure, then pulmonary pathology became more severe as pulmonary pressures approached the systemic pressure.

Lung biopsy grades agreed with the subsequent autopsy grades if at least 1 cm. blocks were available.

This study makes available for the first time lung tissues from patients who have survived intracardiac surgery for closure of ventricular septal defects. Although many other factors undoubtedly affect immediate and prolonged prognosis from surgery, in the present state of our knowledge, pulmonary vascular pathology appears to be the most important single item. It is felt that the "margin for error" is diminished in the face of moderate pulmonary changes graded as 1 and 2. In patients showing nearly balanced pulmonary artery and systemic pressures, lung biopsy may be considered as a preliminary procedure which is justified to avoid major surgery with little hope of survival.

Other attempted correlations between pulmonary pathology and the degree of growth failure, defect size and defect location will be discussed if time permits.

Hg^{203}-Labeled Mercaptomerin Studies in Animals and Humans

Jerry K. Aikawa† and Reginald H. Fitz, Denver, Colo.

The organic mercurial diuretic agent, mercaptomerin sodium, was tagged with the radioactive isotope, Hg^{203}, and was administered parenterally and per rectum to rabbits and human beings, the distribution of radioactivity being determined in vitro by direct tissue analysis and in vivo by surface gamma counting.

The intravenous administration to rabbits of 0.1 mg./Kg. Hg as mercaptomerin resulted at 24 hours in a mean concentration of 5.7 μg./Gm. of renal tissue; the next highest concentration was 0.3 μg./Gm. of liver. The total renal content of mercury was 1 per cent of the injected dose; that in the liver was 0.3 per cent. Repeated injections resulted in a renal cumulative effect. Normal rabbits excreted in the urine 68 to 99 per cent of the injected radioactivity within 24 hours.

The urinary excretion of the material in humans was comparable. Tissues were obtained at autopsy in 8 individuals injected with the tagged mercurial. Renal concentration (6.3 to 69.9 μg. Hg/Gm. of tissue) was at least 4 times greater than in any other tissue. No renal concentration occurred in 1 individual who died anuric. The lack of diuresis from mercurials in subjects with diseased kidney may in part be due to this inability to concentrate mercury.

Tagged mercaptomerin in suppository form was given to 13 subjects, 8 without and 5 with congestive failure. Urinary concentration of radioactivity paralleled its serum concentration and was maximal between 6 and 12 hours. The maximum serum concentration of Hg attained in any subject was 0.46 μg./ml. Renal excretion of 3 per cent of the total administered radioactivity, equivalent to 4 mg. of Hg, was necessary to induce diuresis. One subject in each group showed a diuresis and these 2 showed the largest amount of renal excretion of mercury.

Isotopic Studies of Changes in Body Composition Induced by Steroid Therapy of Rheumatic Fever

Jerry K. Aikawa,† Denver, Colo.

The signs of hyperadrenalism produced during the prolonged treatment of rheumatic children with

corticotrophin or cortisone is thought not to be due primarily to a retention or redistribution of water and electrolytes.

Serial in vivo measurements of the exchangeable sodium content (Na_e) by the radioisotopic dilution technic were made in 11 children with acute rheumatic manifestations treated with adrenocorticotrophin in an initial dosage of 2.0 to 5.7 units/Kg. and continued for 34 to 90 days. All but 1 developed the typical clinical signs of hyperadrenalism. A progressive increase in body weight up to a maximum to 65 per cent of the initial weight was observed. Nine of the 11 showed at least a 10 per cent increase in body weight which was out of proportion to the changes in Na_e, and which could not be explained solely on the basis of a retention of sodium.

Serial measurements of the exchangeable potassium content (K_e) were made in another group of 12 rheumatics given cortisone in an initial dosage of 5.5 to 9.4 mg./Kg. and continued for 58 to 113 days. Seven of 12 developed obvious hyperadrenalism. Eleven showed at least a 10 per cent increase in body weight, the maximum being 50 per cent. All but 1 initial K_e/wt. values were within the normal range; the 7 subjects with hyperadrenalism showed a consistent decrease in the values for K_e/wt. the longer therapy was continued.

The Na_e study suggests that the increase in body weight and the appearance of hyperadrenalism during corticotrophin therapy is not due solely to a retention of sodium; the K_e study suggests that, during cortisone therapy, these changes are not directly related to alterations in body muscle mass. The data are consistent with the interpretation that body fat content is increased.

Electrocardiographic Effects Produced by the Rapid Infusion of One Molar Sodium Lactate and Potassium Chloride in Young Recruits with Acute Rheumatic Fever

Carl S. Alexander and Richard C. Bates, Great Lakes, Ill.

Prompted by the recent reports of Bellet, the electrocardiographic effects of 1 M sodium lactate and/or 40 mEq. of potassium chloride in 1 L. of 5 per cent glucose in water administered intravenously were observed in 20 young males with acute rheumatic fever as established by Jones' criteria. In most cases the control tracing showed some abnormality in A-V conduction, rhythm, or Qt_c prolongation.

The rapid infusion of lactate (usually at a rate of 200 mEq./10 min.) regularly resulted in symptoms of mild tetany. The significant electrocardiographic effects consisted primarily of unpredictable changes in A-V conduction and rhythm disturbances. For example, in 3 patients respectively: (1) interference dissociation was temporarily restored to sinus rhythm after the administration of 160 mEq. of lactate in 8 min., (2) first degree A-V block was temporarily changed to nodal rhythm, and (3) 2:1 A-V block was changed to complete A-V dissociation after the infusion of 100 mEq. in 4 min. Prolongation of Qt_c and reduction in T amplitude were frequently observed after lactate administration.

In contrast, potassium chloride administration affected A-V conduction and rhythm less often; however, increase in T amplitude was consistently observed. In 1 patient the PR interval increased from .18 to .26 sec. and T amplitude increased from .3 mm. to 2.0 mm. Sodium chloride in the same concentration had no effect.

Serum sodium and potassium were determined in most instances just before and at the end of lactate and/or potassium chloride infusion. There was no clear correlation between serum electrolyte levels and electrocardiographic effects. In some cases potassium chloride infusion resulted in a considerable rise in serum potassium and fall in serum sodium.

Protection Against Congestive Heart Failure by Adaptation to High Arterial Pressure

Natalie Alexander, Los Angeles, Calif.

Congestive heart failure can be induced in rabbits by reducing the diameter of the abdominal aorta to about ¼ the original diameter with a Goldblatt clamp placed just proximal to the superior mesenteric artery (Circulation Research **1:** 491, 1953). Two or 3 days after operation, arterial pressure begins to rise rapidly in the upper part of the body. Following development of hypertension, signs of congestive heart failure and death occur. However, the survival time is variable. For example, in a group of 42 male rabbits, 60 per cent died within 5 to 7 days, 26 per cent in 8 to 29 days (average, 10 days), and 14 per cent lived 30 days or more. These differences in survival time suggested an individual variation in the ability of hearts to adapt to a rapidly rising pressure. The present study was done to find out whether successful cardiac adaptation to elevated pressures could prevent the occurrence of congestive heart failure in this type of animal preparation. A 3-stage procedure was used: 1. A Goldblatt clamp was applied to the aorta and a less severe constriction was used than that described above. Thus arterial pressure rose more slowly, and a high level was reached in 7 to 10 days. 2. Thereupon the clamp was unscrewed to remove the stricture. Arterial pressure gradually decreased and leveled off at normal or slightly above normal values within 1 week. 3. The clamp was then screwed down to the size stricture already described for eliciting congestive heart failure in 60 per cent of animals by 5 to 7 days. Arterial pressure rose rapidly, but now animals lived 30 days or more until they were sacrificed. The mechanism involved in cardiac adaptation and resistance to heart failure will be discussed.

A Controlled Study Comparing the Side Effects of Aminometramide, Aminophylline and Placebo

Ralph W. Alexander and Paul O. Greeley, Los Angeles, Calif.

Five hundred fifty-seven patients have been studied for the occurrence of side effects during the administration of aminometramide, aminophylline and placebo. All tablets were of identical appearance and were dispensed 250 mg. 4 times a day for 3 days without the knowledge by either patient or physician as to which compound was used.

Side effects occurred in 12.1 per cent with placebo, 17.2 per cent with aminometramide, and 25.9 per cent with aminophylline. Specific side effects were analyzed as to type and incidence. The most common side effect was nausea which occurred in 9.4 per cent with placebo, 11.9 per cent with aminometramide, and 21.6 per cent with aminophylline. This was followed by vomiting which occurred in 3.4 per cent with placebo, 3.3 per cent with aminometramide, and 7.8 per cent with aminophylline. All cases of vomiting occurred in the nausea group. Other side effects include dizziness, headache, tachycardia, nervousness, choking, insomnia, abdominal cramps and diarrhea. The report shows that the frequency of side effects with aminometramide approaches that with placebo administration but is markedly less than is found with aminophylline.

The report also points out the importance of running a placebo group when testing any medication, preferably utilizing the "double-blindfold" technic.

Incomplete Right Bundle-Branch Block: A Diagnostic Evaluation Using the Direct Spatial Vectorcardiogram

Bertram J. Allenstein, Los Angeles, Calif.

Ninety-four patients, 52 males and 42 females, in whom electrocardiograms demonstrated incomplete right bundle-branch block, were studied with direct spatial vectorcardiograms. The Grishman and the Kimura placements of electrodes were both used. The ages varied from 8 months to 82 years. Forty-three had signs and/or symptoms of heart disease. Twenty-five patients had cardiac catheterization, and 15 had cardiac surgery, after the vectorcardiograms were recorded. All patients had a detailed history, chest x-rays, and a complete physical examination. Most of the patients had cardiac fluoroscopic examinations. Postmortem examination was obtained in 8 patients. The following conditions were demonstrated to be responsible for production of the electrocardiographic record of incomplete right bundle-branch block:

Thirty-five patients had a nonpathologic variation of the normal ventricular conduction pathway; 13 demonstrated actual conduction block of the right bundle; 25 demonstrated right ventricular hypertrophy; 4 had right ventricular hypertrophy and right bundle-branch block; 7 had left ventricular hypertrophy; 5 had combined left and right ventricular hypertrophy, and 5 had myocardial infarction. Illustrations of all the described conditions will be shown.

This study demonstrated that the electrocardiographic record of incomplete right bundle-branch block comprises a heterogeneous grouping, that the direct spatial vectorcardiogram is helpful in clarifying certain electrocardiographic configurations, and that there is advantage to using 2 electrode placement systems.

A Biologic Test for Digitalis Effect

Sidney R. Arbeit and Pierre Moret, Jersey City, N. J.

The ballistocardiogram is consistently abnormal in congestive heart failure. It is frequently abnormal in patients with longstanding hypertension even though they are not in failure. These abnormal traces can be converted to normal, or near normal, by an adequate dose of digitalis.

Parallel studies on dogs showed that when the peripheral resistance was increased by suitable drugs the applied cardiac contractile force was depressed and the ballistocardiogram deteriorated. Digitalization increased the contractile force in spite of the maintained peripheral resistance and the ballistocardiogram reverted to normal. The normalized ballistocardiogram is evidence for the restored balance between the cardiac propulsive force and the resistive forces (load) in the cardiovascular system.

In both studies it was felt that the ballistocardiogram measured the direct effect of digitalis on the heart muscle. The smallest amount of the drug required to produce the normal ballistocardiogram can be looked upon as the minimal therapeutically active dose for that patient at that time.

In this phase of the study the method was used to compare the therapeutic ranges of 2 cardiac glucosides. A later application was the determination of the minimal digitalis requirements of various grades of cardiac decompensation.

Recurrent Mitral Stenosis

Charles P. Bailey and Harry Goldberg, Philadelphia, Pa.

Over the past several years, sporadic reports of apparent recurrence of mitral stenosis, following initially successful surgery, have been appearing in the medical literature. In most cases, there has remained some doubt either that a satisfactory mobilization of the valve had been accomplished, or that a true restenosis had taken place. Especial doubt has been expressed that refusion, surgically, of separated

leaflet surfaces will take place although in many extremely pathologic valves, the very rigidity of the fibrosed or calcified leaflets might contribute to effect a serious degree of impedance to blood flow.

We now can confirm in our own operating series indubitable re establishment of stenosis in patients who have undergone at least an apparently reasonably adequate mitral commissurotomy. In 6 patients, autopsy evidence is available. In 11 others, reoperation and hence digital re-examination of the valve by the original operating surgeon has seemed to offer sufficient proof of the development of such recurrent stenosis. In 3 patients, the information gleaned from left heart catheterization has served to establish the existence of severe mitral obstruction prior to reoperation.

In this series, not only has the valve orifice become narrowed subsequent to clinically (and usually technically) satisfactory mobilization, but reobliteration of the surgically separated commissures also has been evident.

The possible and probable causes of such recurrent obstruction of the mitral valve are discussed. In general, it would seem that recurrent bouts of acute rheumatic activity, continuation of a low-grade or smouldering rheumatic state, incomplete surgical mobilization of the valve structure at the initial operation, or an extreme pathologic state of the valve simulating that of a fibrous stricture are the basic factors to be considered in the development of restenosis. An attempt is made to indite the primarily effective etiologic agent in each clinical case of this series.

Clinical Evaluation of the Surgical Management of Aortic Stenosis

Charles P. Bailey and William Likoff, Philadelphia, Pa.

Three surgical methods are available for the correction of aortic stenosis. Each is based on the principle that the orifice of a stenotic valve can be expanded safely by separating the fused leaflets along the lines of anatomic cleavage.

Two of the technics, transventricular and transaortic commissurotomy, are practiced in the closed heart and have been established sufficiently long for statistical evaluation. The third is a most recent procedure involving the problems associated with open heart surgery.

This communication analyzes these methods in terms of operative mortality and clinical manifestations revealed during long-term survival extending to 5 years. The transaortic and open heart technics are additionally evaluated by left heart catheterization.

The material is derived from 287 patients operated between April, 1952, and February, 1956, by the closed heart technics, and from 4 patients operated by the open heart method. It includes 178 patients (group I) subjected to aortic commissurotomy, and 109 patients (group II) who required simultaneous aortic and mitral commissurotomies.

Although the operative mortality of the transaortic technic is approximately one half of the transventricular, the number of late deaths, the average time of their occurrence, and the postoperative clinical response all contribute toward equalizing the value of both procedures.

The striking clinical improvement enjoyed by the majority of surviving patients extend into such basic complaints as angina, syncope and dyspnea. However, these are counter-balanced by limited alterations in objective findings and by definite evidence of postoperative residual stenosis as determined by left heart catheterization data.

These latter issues emphasize the wisdom of current interest in open heart technics and the logical hope for a more perfect means of attaining better anatomic correction regardless of the magnitude of the morphologic changes at the valve site.

Pericardial Valve Grafts in the Surgical Therapy of Mitral Insufficiency

Alvin A. Bakst and Leo Loewe, Brooklyn, N. Y.

Severe rheumatic mitral insufficiency seems to be due to 2 related factors: a deficiency in valve substance of the mural leaflet at the posterior commissure, and a dilatation of the annulus fibrosis. Apparently, these 2 factors are intimately related, the dilatation of the annulus being secondary to an initial deficiency in valve substance.

Utilizing the concept that mitral regurgitation is due to an initial deficiency of valve substance, the authors have attempted to create and treat this lesion with an engrafted valve leaflet, fashioned from the pericardium.

In a series of animals, mitral insufficiency was created by extirpating the posterior third of the mural leaflet of the mitral valve. In all animals, a significant mitral insufficiency was immediately produced, resulting in a 100 per cent mortality within 24 hours.

In a second group of animals, mitral insufficiency was similarly created at the posterior commissure. Immediately thereafter, a valve graft was inserted into the region of the posterior commissure and the posterior half of the mitral valve. Almost all of these animals survived the procedure.

Simultaneous pressures taken from the left atrium and the left ventricle before and after each phase of the procedure demonstrate the disappearance of the mitral regurgitant pressure curve after the insertion of the free pericardial valve graft. The specimens obtained at sacrifice 6 months postoperatively, reveal complete "take" of these pericardial valve grafts.

Use of Simultaneous Left Atrial, Left Ventricular, and Aortic Pressure Measurements in Evaluating the Effects of Aortic and Mitral Valvular Surgery

Alvin A. Bakst, Clifford Cohen, and Leo Loewe, Brooklyn, N. Y.

The hemodynamic effectiveness of aortic dilatation has been determined by simultaneously measuring pressures from the left ventricle and aorta at the operating table, before and after valvular surgery. This technic permits an objective physiologic evaluation of the results of the operative procedure. Moreover, it provides an excellent means of evaluating the hemodynamic significance of an aortic murmur.

Left atrial, left ventricular, and aortic pressures are obtained by needle puncture in the open chest, and are recorded simultaneously and synchronously with manometers of equal sensitivity and with identical baselines. This provides a graphic record of the pressure changes, as well as an accurate timing of the phases of the cardiac cycle.

In patients with aortic stenosis, there is a significant gradient between the systolic pressures of the aorta and left ventricle, as well as a delay between their peaks of systole. The measurement of this pressure gradient at the operating table provides an accurate means of evaluating the severity of the lesion. This differential in pressure gradient is significantly reduced after effective aortic dilatation.

In other patients clinically diagnosed as combined mitral and aortic stenosis, pressure tracings taken at time of surgery revealed no ventricular-aortic pressure gradient, thus demonstrating the absence of a physiologically significant aortic stenosis. The abandonment of the aortic dilatation diminished the risk attended by a bivalvular procedure.

Patients with pure mitral stenosis reveal an atrial-ventricular end diastolic pressure gradient, which is abolished by adequate mitral commissurotomy.

Clinical and Physiologic Studies Before and After Closure of Atrial Septal Defect

Fouad A. Bashour and C. Paul Winchell, Minneapolis, Minn.

Fourteen adult patients were studied before and after closure of atrial septal defect. The surgical procedure was done under hypothermia. The preoperative diagnosis was established by cardiac catheterization. In 2 patients the presence of mitral valvular disease was noted at surgery.

Physiologic studies of these patients were repeated 3 to 61 months following surgery in order to evaluate the completeness of the closure and to determine the resulting hemodynamic changes.

In 2 cases a small left-to-right shunt persisted due to, in the first case, an anomalous pulmonary venous drainage which was not detected at surgery, and, in the second case, to an incomplete surgical repair of the defect. In both cases a decrease in the magnitude of the shunt resulted in obvious clinical improvement. In the remaining 12 cases, closure of the defect was complete and resulted in marked clinical improvement, and a return to normal functional status.

Significant hemodynamic changes occurred following surgical repair. These included a marked decrease in the pulmonary blood flow, pulmonary arterial oxygen saturation and right ventricular work. A marked increase in the pulmonary vascular resistance was noted in 12 cases after complete repair of the defect, a decrease and only a slight increase were observed in two cases. No significant change in the oxygen consumption was noted. The significance of these findings will be discussed.

Effects of Molar Sodium Lactate in Reversing the Cardiotoxic Effect of Hyperpotassemia

Samuel Bellet, Fred Wasserman, and Jerome Brody, Philadelphia, Pa.

Hyperpotassemia kills primarily by its cardiotoxic effect. Because of the similarity of the terminal cardiac mechanisms in hyperpotassemia to those successfully treated by molar sodium lactate, and because of the rapid effect of this solution in lowering the extracellular potassium, it was felt that molar sodium lactate would be efficacious in treating this state.

Ten patients with advanced cardiotoxic manifestations were treated. Many of these patients were moribund with an unobtainable blood pressure, the electrocardiograms showed a slow irregular rhythm with widened ventricular complexes, and in some cases the complexes resembled those of ventricular flutter. In general, the electrocardiograms resembled the terminal tracings in the dying heart. The serum potassium values before treatment ranged from 7.5 to 10.8 mEq./L.

The dose of sodium lactate ranged from 100 to 350 mEq. administered intravenously over a period of from 5 min. to 3 hours. The effects were dramatic. Marked improvement was observed within 5 to 30 min. depending on the dose and speed of administration. The blood pressure returned to a more normal value and there was a general improvement in the clinical state of the patient. Coincidentally the electrocardiograms showed a return from the bizarre QRS complexes to a normal or a relatively normal configuration.

The improvement was maintained for varying periods of time, depending upon the underlying cause of the hyperkalemia. Molar sodium lactate was found clinically and experimentally to be superior in many respects to the other measures

commonly employed, i.e., sodium chloride, calcium, sodium bicarbonate, and glucose and insulin.

It is felt that the use of molar sodium lactate is an important adjunct in the armamentarium of the treatment of hyperpotassemia. The rapidity of its effect, ease of administration, and relative freedom from toxicity gives this preparation a high priority in the therapy of this state. The mechanism of these effects will be discussed.

Molecular Hypothesis for the Mechanism of Action of Mercurial Diuretics

Reinhold Benesch and Ruth E. Benesch, Woods Hole, Mass.

It is proposed that mercurial diuretics exert their pharmacologic effect by interacting with dithiol chemoreceptors in the renal tubule. These dithiols could be either in the form of lipoic acid or spatially adjacent protein —SH groups. This hypothesis is based on previous chemical studies on the reaction of organic mercurials with mono- and dithiols (Benesch and Benesch, Arch. Biochem. **38:** 425, 1952). It was found that only organic mercury compounds of the mercurated allylamide type react with dithiols in a pH dependent reaction to form an undissociated cyclic mercury mercaptide. The proposed mechanism of action accounts for a number of known facts about these drugs which have been difficult to explain hitherto: 1. Among the compounds investigated, there is a complete correlation between diuretic activity and the ability to form a cyclic mercaptide with dithiols. 2. Monothiols, such as cysteine, glutathione and thioglycollic acid, do not suppress mercurial diuresis in contrast to dithiols. Thus mercaptomerin is diuretic, while BAL completely abolishes mercurial diuresis. 3. Acidifying salts potentiate mercurial diuresis synergistically, while alkalinization inhibits it. This would be predicted from our findings on the reaction between mercurial diuretics and dithiols, since this reaction proceeds 10 times faster for each unit decrease in pH. 4. Even the diuretic action of mercuric chloride is in agreement with the postulated mechanism, since it can form a cyclic mercaptide with dithiols directly.

Contractile Proteins of the Failing Myocardium as Studied with Glycerol-Extracted Muscle Preparations

Ellis S. Benson and Ben E. Hallaway, Minneapolis, Minn.

Glycerol-extracted trabecular muscle bundles were prepared by the method of Szent-Györgyi (Biol. Bull. **96:** 140, 1949) from the right and left ventricles of 12 adult mongrel dogs, 7 of which were in chronic congestive failure secondary to surgically produced pulmonary stenosis and tricuspid insufficiency, and the remaining 5 normal controls. Fine bundles, 0.7 to 1.5 cm. long and 0.1–0.2 mm. in diameter, were mounted in an isometric myograph, a modification of that described by Ranney (J. Appl. Physiol. **6:** 513, 1954), and placed in a bath containing 0.05 M KCl and 0.005 M $MgCl_2$ buffered at pH 8.2 with trishydroxymethyl-aminomethane. On contraction with adenosinetriphosphate (4.6 mM/L.) tension developed and was measured under isometric conditions at 25 C. Diameter of the fibers was computed by protein determination. Fibers from normal right ventricles developed tension of 2.5 to 3.7 Gm., mean 3.0 Gm./mm.^{2} cross-sectional area; those from failing right ventricles 1.1 to 2.4 Gm., mean 1.6 Gm. For normal left ventricles, the equivalent values were 3.0 to 4.0 Gm., mean 3.3 Gm., and for failing left ventricles 2.1 to 2.8 Gm., mean 2.4 Gm. Fibers from failing hearts showed the same degree of isotonic shortening as normal fibers (60 to 70 per cent). Contractile tension at any length, and therefore working capacity was lower for fibers from failing hearts than those from normal hearts. Since in these fibers the contractile proteins are isolated from membrane effects, energy-supplying systems, and from electrolyte and pH effects, these latter being controlled, decreased contractile tension of the failing myocardium may be ascribed to physicochemical changes in the contractile proteins.

Tietze's Syndrome

Michael Bernreiter, Kansas City, Mo.

Tietze's syndrome is a painful nonsuppurative swelling of the costochondral or sternoclavicular junction. Since Tietze's original description in 1921, over 100 patients with chest pain caused by this syndrome have been described by foreign authors. It has been described only twice in the American literature.

In the differential diagnosis of chest pain, Tietze's syndrome should always be considered. Tenderness over the involved cartilage is at times extreme and may be exaggerated by effort as result of increased thoracic movement. A small firm smooth mass may become palpable and visible in the involved costochondral junction.

Etiology of this syndrome is not known. Malnutrition, heavy lifting, repeated trauma from cough and sudden movements have been described as causative factors. The second costochondral junction is involved in about 60 per cent of all cases. The presence of an interarticular sternocostal ligament in this area suggests that trauma or rheumatic disease of this ligament may be an important factor in the etiology of this syndrome. No specific findings have been reported on x-ray examination, but radiologic examinations and other laboratory tests may be quite helpful in excluding associated diseases producing chest pain. Tietze's syndrome is quite easily recognized if one just

thinks of this possibility. In the differential diagnosis one must consider benign and malignant diseases within the chest wall, in the breasts, the lungs, heart, and mediastinum.

The treatment in the past consisted of local applications of heat, salicylates, procaine infiltrations, and reassurance of the benign character of the disease. The treatment in the 6 cases of Tietze's syndrome herewith reported consisted of oral cortisone and this seemed more specific than any therapy previously instituted.

Unusual Electrocardiographic Findings in Cardiac Amyloidosis

Michael Bernreiter, Kansas City, Mo.

Three cases of severe cardiac amyloidosis with autopsy findings are reported. Low QRS and T wave voltage, particularly in the extremity leads and changes in the precordial leads, suggestive of myocardial scarring, have been reported by others and were present in this case.

Electric alternation of the P waves has, to my knowledge, not previously been reported in connection with amyloidosis of the myocardium. It was an outstanding finding in our cases and, in connection with voltage lowering and suggestive infarct patterns, may constitute a helpful triad in this otherwise difficult diagnosis.

Observations on the Mechanism of the Hypocholesterolemic Effect of Sitosterol

Maurice M. Best and Charles H. Duncan, Louisville, Ky.

The plant sterol, sitosterol, has been reported to exert a hypocholesterolemic effect in man on unrestricted diet, a mean reduction of 16 per cent occurring in our series. Some light is shed on the mechanism of this effect by the animal studies to be reported.

When 1 per cent cholesterol is added to the diet of the albino rat, a sufficient amount is absorbed to result in a fourfold increase in liver cholesterol in 2 weeks (303 ± 6 mg./100 Gm. liver to 1109 ± 285). The further addition to the diet of 5 per cent sitosterol interferes with cholesterol absorption to such a degree as to completely prevent this rise in liver cholesterol, the level at the end of 2 weeks (271 ± 39 mg./100 Gm. liver), being essentially the same as that obtained with a cholesterol free diet. In the hypothyroid state, the effect of increased absorption of cholesterol (cholesterol feeding) and of preventing this absorption (addition of sitosterol to the diet) are exaggerated as a result of the reduced rate of turnover of cholesterol.

Using the rat subjected to radiation destruction of the thyroid by iodine^{131} the effects of prior esterification of cholesterol and of sitosterol have been studied. It was found that cholesteryl palmitate, was much less readily absorbed than equimolar amounts of the free sterol (liver cholesterol of 357 ± 54 mg./100 Gm. liver as compared to 1625 ± 296 for free cholesterol). Similarly, sitosterol palmitate was relatively ineffective in inhibiting cholesterol absorption (liver cholesterol of 1259 ± 415 mg./100 Gm. liver as compared to 281 ± 28 with free sitosterol). These findings suggest that esterification is an active step in cholesterol absorption and sitosterol might act by tying up the esterification mechanism, perhaps by competing with cholesterol for esterification.

Simple Technic Using Orthostatic and Valsalva Maneuvers to Prove the Existence of the Electrocardiographic Unstable T Wave

Edward W. Bixby, Jr., Philadelphia, Pa.

With the vast numbers of electrocardiograms being taken at the present time, the incidence of iatrogenic electrocardiographic heart disease is a pressing problem. Tracings which are unusual but not definitely pathologic are easily misleading, even to those well trained in electrocardiography.

Methods to identify innocent though alarming variation from the normal using ergot preparations, the nitrites, inflated suits, bandages and water immersion were described by Wendkos and Logue in 1946. Application of these tests is time-consuming, cumbersome, disturbing and occasionally dangerous to the patient.

A simple, rapid and harmless technic, using the standing position and Valsalva maneuver while recording the electrocardiogram will identify most, if not all, instances of the unstable T wave syndrome. It has been shown in a series of 75 cases that instability of the T wave neither includes nor excludes the presence of organic heart disease.

Severe Aortic Regurgitation in Young People: A Long-Term Perspective with Reference to Prognosis and Prosthesis

Edward F. Bland and Edwin O. Wheeler, Boston, Mass.

A review is presented of the long-term studies of rheumatic heart disease at the House of the Good Samaritan in Boston with reference to the incidence and course of severe aortic regurgitation in young patients.

The over-all series comprises 2,000 consecutive patients studied in the 2 decades between 1921 and 1943 and their subsequent course. There were 87 patients whose principal valve deformity was aortic regurgitation of high degree. Males outnumbered females by 2 to 1.

The after-history of these 87 patients was both revealing and surprising, in that at the end of 10 years a third (37 per cent) were still able to lead quiet, more or less comfortable lives, and at the

end of 20 years a fourth (26 per cent) remained in this favorable category. On the other hand, 38 per cent succumbed in 10 years and 56 per cent in 20 years.

The ominous significance of a special and atypical clinical syndrome is emphasized as an indication for surgical intervention.

A limited experience with the plastic valve of Hufnagel is presented, with favorable results in 40 per cent and extraordinary benefits in a few. This physiologic compromise seems justified for those in serious difficulty until a more promising procedure is available.

Carotenoid Pigments Found in Human Atherosclerosis

David H. Blankenhorn, Cincinnati, Ohio, David G. Freiman, Boston, Mass., and Harvey C. Knowles, Jr., Cincinnati, Ohio.

Carotenoid pigments are red- and yellow-colored paraffin hydrocarbons. They are lipids known to be derived exclusively from dietary sources. In 1934, Aschoff reported the occurrence of these compounds in the lesions of atherosclerosis, but this finding has received little attention.

A study of the carotenoid content of 30 human aortas has shown that carotenoids are found in direct proportion to the severity of the atherosclerotic lesions encountered. The yellow color of early lesions gives evidence of their pigment content. More advanced lesions contain even greater amounts of carotenoids which may be masked by fibrosis, ulceration, or other factors.

The increase in carotenoids parallels an increase in cholesterol content encountered with increasing severity of atherosclerosis. A dietary lipid has been shown to accumulate in the human aorta in direct proportion to the severity of atherosclerotic lesions and to the content of cholesterol.

Determination and Significance of Serum Glycoprotein. I. Hexosamine in Degenerative Vascular Disease Associated with Diabetes Mellitus

J. M. B. Bloodworth, Jr., and George J. Hamwi, Columbus, Ohio.

Protein-carbohydrate complexes (glycoproteins) have been frequently associated with degenerative vascular disease The carbohydrate moiety of glycoprotein, contains a high concentration of hexosamine. Pure hexosamine can be measured by reaction with acetylacetone followed by color development with Erlich's reagent. Unfortunately this procedure (the Elson-Morgan method) cannot be applied directly to plasma of diabetic patients because of the interference of plasma glucose. Previous reports are contradictory but our studies show conclusively that glucose produces a color when assayed by the Elson-Morgan technic. Mixtures of glucose and glucosamine are additive in low concentrations but when glucose concentrations similar to those seen in diabetes mellitus are reached there is a suppressive effect often resulting in less color than produced by glucosamine alone. Other plasma variables such as amino acids, urea, chloride and phosphate salts produced no effect on the determination. We have prepared plasma proteins which are essentially free of reducing substances by heating plasma for 5 min. at 100 C. and pH 1.9 followed by the addition of 10 volumes of ethanol to the supernatant. Hexosamine is liberated by acid hydrolysis. Unfortunately acid hydrolysis also destroys some of the free hexosamine. Our data show that hydrolysis for 2 hours in 4 N acid gives highest yield. The hydrolysate is then neutralized and the Elson-Morgan method applied. The results show that plasma protein-bound hexosamine is lowest in normal ambulatory medical students. Diabetic patients show a significant increase when compared to medical students but bed-ridden hospital patients with normal carbohydrate metabolism show a similar elevation of the hexosamine level. These studies indicate that previously reported elevations in the serum hexosamine level may be due to nonspecific factors completely unrelated to diabetes mellitus.

Effect of l-Norepinephrine upon the Isolated Beating Mammalian Heart

Walter L. Bloom and Noble O. Fowler, Atlanta, Ga.

White rats (Sprague-Dawley) were anesthetized with intraperitoneal Nembutal, 6 mg./100 Gm.

The beating heart was quickly removed and immersed in saline or lactate-Ringer's solution at room temperature. Left ventricular pressures were recorded with simultaneous electrocardiograms before, during, and after addition of 5–10 γ of l-norepinephrine to the 500 ml. bath. If the left atrium was removed, a control systolic pressure of 11–84 mm. water was recorded during ejection of fluid followed by a negative diastolic pressure of −2 to −22 mm. water, as the ventricle filled by suction. With an intact left atrium, its valve-like action prevented entrance of fluid into the heart, and because of the diastolic sucking action of the left ventricle, the intraventricular pressure was chiefly negative, maximally in early diastole.

Sixteen hearts were studied. Control heart rates were 38–112/min., mean 64.5. After l-norepinephrine, heart rates were 40–154/min., mean 91.4. Increases ranged from 6 to 82/min. Five of 6 hearts failed to show an increase in rate. Systolic pressures increased in 8 hearts with atria removed from 11–40 mm. H_2O, mean 21.8, before l-norepinephrine, to 20–58 mm. H_2O, mean 38 afterward. Diastolic pressures were adequately recorded in 9 hearts, including 3 with intact left atrium;

pressures were −2 to −13 mm. H_2O, mean −7.4 before and −2 to −22, mean −13 mm. H_2O, after l-norepinephrine. Five hearts failed to show an increase in pressure after l-norepinephrine; only 2 showed no increase in rate or pressure, possibly because of anesthetic depression.

It is concluded that l-norepinephrine has direct inotropic and chronotropic action on the isolated beating mammalian heart and is capable of increasing both systolic force of fluid propulsion and diastolic action of sucking.

Ebstein's Anomaly

S. Gilbert Blount, Jr., Malcolm C. McCord,‡ and Irvin J. Gelb, Denver, Colo.

The purpose of this communication is to present clinical and hemodynamic data from 4 patients with Ebstein's anomaly. Two patients represent the classical picture of the lesion in childhood. The remaining 2 patients are acyanotic adults presenting clinical features suggesting acquired valvular heart disease. Emphasis is placed on the elements aiding in the establishment of a diagnosis in this latter group.

The electrocardiogram offers valuable diagnostic aid in patients with Ebstein's anomaly. A classical feature which occurs in a high percentage of cases is a complete right bundle-branch pattern with low amplitude R waves in the right precordial leads. The serial electrocardiograms of 1 child from 2 weeks of age until 5 years demonstrate the development of a right bundle-branch block pattern. This suggests the development to be secondary to the deformity of the tricuspid valve and not to be of congenital origin.

Enlargement of the right atrium is the dominant radiologic feature. Bulging of the right ventricular outflow tract and the pulmonary arterial pattern are also characteristic findings.

Cardiac catheterization continues to be the most effective means of confirming the presence of this entity. The principal features consist of a greatly enlarged right atrium, a displacement of the tricuspid valve to the left, a normal right ventricular, pulmonary arterial and pulmonary arterial wedge pressure, and an absence of an arteriovenous shunt.

Pressure patterns suggest that the right atrial contraction may affect pulmonary arterial filling and contribute to the propulsion of blood into the pulmonary arterial system. However, cardiac catheterization studies will not be diagnostic of Ebstein's anomaly unless the clinician includes this congenital defect in the precatheterization differential diagnosis.

‡Deceased.

Complete Anomalous Pulmonary Venous Drainage in Infancy

Sidney Blumenthal, William Blanc, and Sylvia P. Griffiths, New York, N. Y.

Complete anomalous pulmonary venous drainage is a relatively uncommon anomaly associated with marked hemodynamic alterations so that a fatal outcome during infancy has been reported in 80 per cent of such instances. Successful surgical correction associated with the use of extracorporeal circulation has been reported.

We have reviewed the clinical course in 7 infants in whom this diagnosis was verified at postmortem examination. All were normal at birth and during the neonatal period. Cyanosis, appearing at about 1 month of age, never became severe. Tachypnea subsequently developed, being often associated with inability to feed properly. When cardiac failure became apparent the subsequent clinical course was rapidly progressive.

Examination usually revealed a small slightly cyanotic infant with a barrel-shaped chest deformity. A murmur was often insignificant or absent. In some a prominent systolic murmur could be heard. The electrocardiograms were at first normal, but as symptoms progressed a right ventricular hypertrophy pattern developed in all patients.

Serial x-ray films of the chest revealed the heart to be normal in size at birth followed by a rapid increase during the next few months. This was associated with the development of a prominent pulmonary artery segment and pulmonary plethora. The cardiac silhouette varied depending upon the site of insertion of the anomalous pulmonary veins. Characteristic changes were observed in a few.

Pathologic findings included marked hypertrophy of the right ventricle with dilatation of the right atrium and hypoplasia of the left atrium. The size of the foramen ovale and site of insertion of the pulmonary veins varied as did the degree of endocardial fibrosis.

The clinical picture often resembled that seen in primary endocardial fibroelastosis except for the cyanosis and right ventricular hypertrophy pattern in the electrocardiogram. Transposition of the great vessels and large atrial septal defects were often considered in the differential diagnosis.

Reaction of an Occluded Artery During Normal and Abnormal Valsalva Responses

Stuart Bondurant and John M. Wallace, Durham, N. C.

The arterial pressure response to the Valsalva maneuver includes a post-Valsalva overshoot not seen in the presence of left ventricular failure, mitral stenosis or disease of the autonomic nervous system. The relative significance of change in

cardiac output and peripheral vascular tone in producing this overshoot has not been clearly defined. Because of recent interest in the clinical use of this phenomenon as a diagnostic test, a series of experiments were undertaken to evaluate the mechanism of the overshoot.

Valsalva maneuvers were performed by 6 normal subjects at rest and after inflation of a balloon type G-suit. Oral pressure of 40 mm. Hg maintained for 15 sec. was the standard Valsalva maneuver. Indwelling needles were used to measure pressure in both brachial arteries, 1 distal to an arterial tourniquet (280 mm. Hg). The hemodynamic isolation of the arterial system distal to the tourniquet was consistently demonstrated by the failure of this system to reflect the increase in systemic pressure always seen with initiation of the Valsalva and G-suit inflation.

In all subjects, arterial pressure response to the control Valsalva included a consistent overshoot (35 ± 12 mm. Hg systolic, and 16 ± 3 mm. Hg diastolic) 3 to 8 sec. after Valsalva release. Three to 5 seconds after beginning the Valsalva, pressure in the isolated artery began an increase which reached a peak of 10 ± 2 mm. Hg coincident with maximum post-Valsalva overshoot.

Valsalvas performed by the same subjects during G-suit inflation were followed by minimal overshoots (3 ± 1 mm. Hg systolic, and 2 ± 1 mm. Hg diastolic) and essentially no change in pressure in the isolated arterial segment.

These findings further establish the role of reflex peripheral vascular constriction in the post-Valsalva overshoot of arterial pressure, and place the clinical use and interpretation of this test on a firmer basis. This technic for study of arterial reactions in man should have additional useful applications.

Electrocardiographic Diagnosis of Ventricular Hypertrophy in the Presence of Right Bundle-Branch Block

Richard W. Booth, Te-Chuan Chou, and Ralph C. Scott, Cincinnati, Ohio.

All the Cincinnati General Hospital postmortem records from the years 1950–55 inclusive were reviewed and all those with electrocardiographic diagnoses of right bundle-branch block (RBBB) subjected to analysis. It was stipulated that a 12-lead electrocardiogram must have been taken within 3 months of death, and all cases with myocardial infarction were discarded. During this 6-year period over 3,000 autopsies were performed and 49 cases fulfilling our criteria were obtained.

Postmortem findings revealed: 4 instances of isolated right ventricular hypertrophy (RVH), 15 of isolated left ventricular hypertrophy (LVH), 22 of combined left and right ventricular hypertrophy (CVH), and 8 with hearts of normal measurements.

Study of the electrocardiograms in 28 cases of incomplete RBBB revealed 8 cases which fulfilled Barker and Valencia's criteria for coexisting RVH, i.e., right precordial R′ > 10 mm. Of these, 2 cases had RVH, 1 LVH, 3 CVH, and 2 no hypertrophy at autopsy. One case met electrocardiogram criteria for LVH but had RVH at postmortem and one revealed CVH on the electrocardiogram but LVH at postmortem. The remaining 18 at autopsy showed LVH in 5, CVH in 11, and no hypertrophy in 2.

The 21 cases of complete RBBB revealed 3 with electrocardiogram evidence of associated RVH, i.e., R′ > 15 mm. over the right precordium. At autopsy 1 had RVH, 1 LVH, and 1 CVH. The remaining 18 had LVH in 7, CVH in 7, and no ventricular hypertrophy in 4.

These results indicate that in our series: 1. Anatomic LVH, either isolated or combined, was consistently masked on electrocardiogram by both complete and incomplete RBBB. 2. Those cases with electrocardiograms which met Barker and Valencia's criteria for coexisting RVH frequently, but not invariably, displayed RVH at postmortem. 3. In 49 cases of etiologically unselected RBBB, only 26 (53 per cent) showed anatomic evidence of either isolated or combined right ventricular hypertrophy.

Studies of Serum Proteins, Lipids and Lipoproteins in Coronary Atherosclerosis

Elaine T. Bossak, Chun-I Wang, and David Adlersberg, New York, N. Y.

The investigation included 2 groups of patients with proven coronary artery disease: (1) with normal levels of serum total cholesterol (limits defined by Keys), and (2) with idiopathic hypercholesteremia. Group A included 34 hospitalized patients: 22 men (mean age 54), and 12 women (mean age 69). In 22 patients acute myocardial infarction occurred an average of 30 days before study; in 12 patients the last infarct had occurred 2½ years before. Group B consisted of 26 patients, of whom 15 were hospitalized. There were 19 men (mean age 51), and 7 women (mean age 49). In 7 patients acute myocardial infarction occurred an average of 19 days before study, in 12 patients the last infarct had occurred 4½ years before, and 7 patients presented angina with appropriate electrocardiographic changes. Xanthoma tendinosa were presented in 6 patients, and eyelid xanthelasma in 3.

Serum protein and lipoprotein components were determined by paper electrophoresis using Amido-schwarz and Oil Red O. Simultaneously, serum total and esterified cholesterol, phospholipids and total lipid were determined by chemical methods. All sera were drawn from fasting patients.

Serum protein patterns in patients from group A

were normal. In group B there was a tendency to a decrease in albumin and increase in β and γ globulins. Mean levels of serum total and esterified cholesterol and phospholipids were not altered in patients from group A (228 mg. per cent, 165 mg. per cent and 256 mg. per cent; control: 211 mg. per cent, 157 mg. per cent and 253 mg. per cent). Levels of triglycerides and total lipid averaged 391 mg. per cent and 875 mg. per cent (control: 196 mg. per cent and 660 mg. per cent). In patients from group B all lipid fractions were higher: mean total cholesterol 373 mg. per cent, esterified cholesterol 264 mg. per cent, phospholipids 350 mg. per cent, triglycerides 443 mg. per cent and total lipid 1166 mg. per cent. There were marked changes in the serum lipoprotein pattern in both groups of patients: α-lipoprotein was depressed (A: 21.6 per cent, B: 19.1 per cent, control: 35.3 per cent), β-lipoprotein increased (A: 61.6 per cent, B: 62.5 per cent, control: 52.3 per cent) and there was some elevation of the origin-fraction (A: 15.8 per cent, B: 18.4 per cent, control: 12.3 per cent).

It is of interest that the patients with coronary artery disease and normal chemical lipid levels presented alterations in lipoprotein pattern similar to those obtained in patients with hypercholesteremia.

Sequence of Ventricular Contraction in Human Bundle-Branch Block

Eugene Braunwald and Andrew G. Morrow, Bethesda, Md.

Simultaneous registration of right and left ventricular pressure pulses with an electrocardiographic lead permits determination of the time of onset of contraction of both ventricles. Should interruption of conduction in 1 of the 2 main bundle-branches exist, the onset of contraction of the ventricle supplied by that branch would be expected to be significantly delayed. Nine patients with electrocardiograms showing bundle-branch block were studied by catheterization of both ventricles. Left heart catheterization was performed by the bronchoscopic technic.

In 4 patients with the electrocardiographic configuration of complete left bundle-branch block, the onset of left ventricular contraction was simultaneous with the onset of right ventricular contraction in 1 patient, preceded the onset of right ventricular contraction by 0.01 sec. in 1 patient, and followed it by 0.01 sec. in 2 patients. In 3 patients with the electrocardiographic configuration of right bundle-branch block, but with clinical and hemodynamic evidence of right ventricular hypertrophy, no abnormal delay in the onset of right ventricular contraction was observed. The observations in these 7 patients are thus not in accord with the concept that in patients with the electrocardiographic configuration termed "bundle-branch block" total interruption of the spread of impulse through the affected bundle occurs. However, in 2 patients with electrocardiograms showing right bundle-branch block, but without clinical or hemodynamic evidence of right ventricular hypertrophy, the onset of right ventricular contraction followed the onset of left ventricular contraction by 0.04 sec., suggesting that a block in the path of conduction to the right ventricle indeed existed.

Oxygen Differentials in the Heart

Bernard L. Brofman, Cleveland, Ohio.

The immediate cause of pain and death in patients with coronary artery disease is poorly defined. There is no obligate correlation between the degree of coronary artery narrowing and the consequences thereof. Electrocardiographic studies in dogs have been carried out using epicardial leads and direct current measurements with nonpolarizable electrodes. Direct epicardial electrocardiograms also have been obtained during operation in patients with coronary artery disease. Four conditions of myocardial oxygenation can be demonstrated.

The uniformly pink well-oxygenated heart and the uniformly blue anoxic heart exhibit isoelectric ST segments throughout, indicating uniform electric potential. These hearts are electrically stable and do not develop ventricular fibrillation. When a coronary artery is ligated, the blue area of myocardium produced is surrounded by well-oxygenated muscle. ST segment elevation occurs over the blue area with an abrupt transition to ST segment depression over the pink area. An oxygen differential exists. The blue poorly-oxygenated area is electrically negative to the pink area. The ST segment deviations are an expression of this difference in electric potential of the 2 contiguous areas. Such a heart is electrically unstable and ventricular fibrillation readily occurs. The uniformly cyanotic heart is capable of continued function. However, when 1 area of this heart is perfused with red blood via a cannulated coronary artery, ST depression occurs over the pink area with ST elevation over the blue area. Again there is an oxygen differential, the heart is electrically unstable and ventricular fibrillation may occur.

The application of these studies to human coronary disease will be discussed along with the mechanisms of benefit provided by operation on patients with coronary disease.

A Method for the Isolation of Cardiac Myofibrils

Arnold L. Brown, Albertas Aras, and George M. Hass, Chicago, Ill.

Methods have been developed for isolation of contractile skeletal myofibrils. Studies of these

myofibrils in vitro have provided some information about the contractile reaction of skeletal muscle. Application of the same methods to cardiac muscle failed to yield myofibrils in sufficient numbers to permit desired studies of their contractile reactions in vitro. Modifications of the procedure for skeletal myofibrils finally led to a method suitable for isolation of large numbers of either skeletal or cardiac myofibrils from human and animal sources. Cardiac myofibrils have thus become available in sufficient quantity to permit simultaneous study of morphologic and substrate changes during contraction in vitro, and to analyze these changes in the presence of myofibrils from the normal or abnormal myocardium. Canine and human hearts were used. Canine hearts were fresh. Human hearts were obtained 2 to 12 hours postmortem. The hearts were perfused with 0.15 M potassium chloride, pH 7, and then stored at −40 C. or milled promptly. Ventricular muscle was used after removal of epicardium, endocardium and chordae tendineae. Blocks of muscle were placed in a 4:1 glycerol-phosphate or TRIS buffer. Then the colloid mill was run for 30 to 60 min. following which a crude suspension of myofibrils became available. This suspension was stored for 1 hour at room temperature and then washed with TRIS buffer (1:4) in potassium chloride. After repeated washing and centrifugation, about 10 per cent of the original muscle was recovered as myofibrils. These possessed normal striations with I bands approximately equal in width to A bands. Addition of ATP to the washed suspensions resulted in prompt contraction of myofibrils with associated liberation of inorganic phosphate. An identical response was obtained by use of appropriate extracts of fresh cardiac or skeletal muscle.

Relations Between Body Build and Electrocardiographic Characteristics

Josef Brozek and Ernst Simonson, Minneapolis, Minn.

The study of the relationships between man's body build and electrocardiogram characteristics is of interest on account of the potential role of individual differences in physique in the development of degenerative heart diseases and associated electrocardiogram changes, and the vexing problem of electrocardiogram standards. Yet the amount of available information is scant and limited to such general characteristics as body weight and height. In the present study, interrelationships between anthropometric and electrocardiogram characteristics were examined in 90 middle-aged, clinically healthy men.

The anthropometric variables served to characterize the size and shape of the chest (5 variables), bony framework (4 variables), and soft-tissue development (relative weight, adiposity, muscularity). The following electrocardiogram variables were considered: (1) scalar—QRS axis and T axis, Σ QRS, Σ T, R_2, T_2; (2) vectorial—azimuth (H^0), elevation (V^0), and magnitude of QRS and T as well as Δ^0 (angle between the 2 spatial vectors). The relationships were examined in terms of Yule's Q coefficient of association and χ^2 test.

Neither the QRS axis in the ordinary electrocardiogram nor the elevation (V^0) of the QRS vector, are affected by the anatomic variations studied. The T axis in conventional electrocardiograms and the elevation of the T vector are most sensitive to somatic differences, statistically significant associations being obtained in 9 and 8 out of 12 comparisons, respectively. Among the anthropometric variables, the absolute and relative width of the chest, relative weight, and thickness of the subscapular skinfold (as a measure of obesity) appear to be the most significant factors in body build affecting electrocardiogram characteristics.

Consideration of the effects of these anthropometric variables will make electrocardiogram standards more precise, and thus improve electrocardiographic interpretation.

Effects of Upright Posture and Exercise (Grade Walking) on Pulmonary Hemodynamics in Patients with Left-to-Right Shunts

Robert A. Bruce and Gregory G. John, Seattle, Wash.

In selecting patients with septal defects or patent ductus arteriosus for surgical treatment, effects of sitting and of physiologic exercise in the upright position were studied in 10 patients. Oxygen consumption, while breathing room air, was determined by gasometer and Scholander technics; total pulmonary blood flow was calculated from differences in pulmonary venous oxygen content (assuming 99 per cent saturation) and Van Slyke-Neill determination of pulmonary arterial oxygen content. Pulmonary arterial pressures were recorded while patients were walking on a treadmill. Ear oximeter and precordial electrocardiogram were monitored continuously. Provided hypotensive effects of initial sedation for catheterization were prevented by prophylactic administration of ephedrine sulfate, none experienced untoward effects other than occasional premature beats in 2 patients.

In contrast to published data on patients without shunts, sitting in a chair increased total pulmonary blood flow from an average of 8.9 to 11.1 L./min. in 4 patients. Walking caused further increments in flow and pressure.

One patient with atrial septal defect increased pulmonary blood flow from 13.1 to 23.5 L./min. during walking. There was moderate hyperventila-

tion, normal ventilation perfusion ratio, and a high pulmonary stroke volume. Total pulmonary vascular resistance decreased from 128 to 40 dynes sec. cm.$^{-5}$. Several patients showed similar changes. One patient exhibited hypoventilation and arterial desaturation. Another with ventricular septal defect had marked hyperventilation and pulmonary hypertension with a high ventilation perfusion ratio (4.3), reduced pulmonary stroke volume, increased pulmonary vascular resistance (1590 dynes sec. cm.$^{-5}$) and arterial desaturation to 83 per cent with exercise.

In conclusion, evaluation of pulmonary hemodynamics in patients with left-to right shunts is incomplete unless responses to posture and exercise are tested.

Therapeutic and Toxic Indices of Digitalis: A Comparative Study of Gitalin and Digitalis Leaf

John W. Bryfogle, Thomas F. Santilli, Herbert A. Saltzman, and Samuel Bellet, Philadelphia, Pa.

Determinations of the therapeutic range of a digitalis preparation in cardiac patients may entail errors due principally to variations in therapeutic and toxic levels in different individuals with various grades of myocardial disease and digitalis sensitivity, and to the lack of a satisfactory objective method of differentiating minimal and maximal therapeutic doses in many patients, especially those with a sinus rhythm. In this study amorphous gitalin, which has been reported to possess a uniquely wide therapeutic range, was compared to a standardized preparation of digitalis leaf, using only objective criteria of effects.

In animals, gitalin was compared by a bioassay procedure with other preparations.

In man, comparison studies were made in a single group of 37 cardiac patients with established atrial fibrillation. Therapeutic maintenance doses were determined using ventricular rates observed after rest, exercise and atropine administration. Toxicity and potency could be related in 13 subjects in whom electrocardiographic evidence of toxicity occurred.

Results indicate that while gitalin has a lethal dose in animals that is 3 to 4 times that of other preparations having a similar recommended dose, observations in man indicate that gitalin (0.5 mg.) and digitalis leaf (0.1 Gm.) are equivalent in therapeutic effect over a wide individual dosage range. In any individual case, a decreased toxicity of 1 preparation over the other was accomplished by a decreased potency and similarly an increased potency was associated with an increased toxicity. A wider therapeutic margin for gitalin could not be demonstrated.

Influence of a Hot and Humid Environment on Cardiac Output and Work in Normal Man and in Patients With Chronic Congestive Heart Failure at Rest

George E. Burch and Albert Hyman, New Orleans, La.

The influence upon cardiac output of hot and humid environments was studied in 3 control subjects and 4 patients with chronic CHF (functional class III). Cardiac output, stroke volume, right ventricular pressure curves, and mean right atrial and systemic venous pressures were obtained by cardiac catheterization. Arterial pressure, respiratory and pulse rates, rectal and skin temperatures, clinical appearance, subjective reactions, tidal air, O_2 consumption, A-V O_2 difference, electrocardiogram, and O_2 saturation of circulating hemoglobin were recorded. From necessary assumptions, time course curves of volume-pressure tension in the wall *of right and left ventricles*, accumulated work, time course of power, etc., of the right and left ventricles were obtained (Circulation **5:** 504, 1952; Am. Heart J. **50:** 352, 1955). Measurements were made at about 73 F. and 60 per cent R.H., then 111 F. and 86 per cent R.H.

Cardiac output was increased by the hot and humid environment from 5.0 to 10.1 L./min. in the control subjects and from 5.2 to 20.4 in those with failure. Mean stroke volume rose from 65.2 to 210 ml. in the controls, and from 69.8 to 100.4 ml. in the subjects with CHF. Configuration of the "loops" of volume-pressure differed considerably for the control and cardiac failure subjects, being more vertical in the latter. Curves of accumulated work were much smaller in magnitude for the subjects with CHF, whereas curves of tension in the ventricular walls reached greater magnitudes in CHF, with exceptions at times for the hot and humid environment.

Hot and humid environment was shown to be a strong stimulant to cardiac output, stroke volume, and work in normal man and man with CHF even at rest. Consideration must be given to environment when advising patients with cardiac disease, chronic disease, debilitating states and old age, especially concerning exercise, clothing, and housing.

Some Factors Affecting Recovery From Stoppage of the Heart and Coronary Flow During Extracorporeal Circulation

John T. Burroughs and David E. Donald, Rochester, Minn.

Extracorporeal circulation with the Gibbon pump-oxygenator was established in 15 dogs. Coronary perfusion was practically eliminated by cross-clamping the ascending aorta; using the technic of Melrose, the heart was stopped for 10 or 40

min. by injection into the base of the aorta of either 4 to 8 ml. of 10 per cent potassium chloride, or 2 to 3 ml. of 25 per cent potassium citrate, each diluted to 50 ml. with oxygenated blood. Recovery was evaluated by electrocardiography, observation of the cardiac action, and the ability of the heart to sustain the circulation after cessation of extracorporeal circulation.

Three factors, duration, residual coronary flow and postrelease cardiac dilatation, greatly influenced the recovery of the heart after re-establishing coronary perfusion. Hearts without coronary flow and in asystole for 10 min. recovered promptly with good cardiac action, whereas hearts stopped 40 minutes recovered slowly with poor cardiac action. In hearts stopped for 40 min., the slightest degree of residual coronary flow profoundly altered recovery. Slight coronary flow persists unless bronchial flow into the left heart is completely excluded. In 8 dogs without complete interruption of bronchial flow the heart fibrillated immediately following release of the aorta. In 4 dogs bronchial flow and hence all residual coronary flow was excluded by tape occlusion of the lung roots. In all 4 there was an immediate co-ordinated rhythm. After 40 min. of asystole, acute dilatation occurs when the extremely large coronary flow occurring on release of the aorta is permitted to collect in the right heart. In 4 dogs, 3 with no provision for pick-up of blood returning to the right heart and 1 with a vent in the right ventricular apex, gross dilatation, mottled cyanosis, and poor recovery occurred. Right ventriculotomy prevented this complication.

Infundibular Dynamics Studied by Cineangiocardiography in Pure Valvular Pulmonary Stenosis

Frank L. Campeti, Rochester, N. Y.

Infundibular mechanics have been studied on high-speed cineangiocardiograms by means of angiocardiometry, electrokymography and densitometry in normal subjects and in 26 cases of valvular pulmonary stenosis (12 uncomplicated).

The curve representing infundibular movement differs from the normal in cases of severe pulmonary valvular stenosis associated with infundibular hypertrophy. The secondary peaks due to rapid inflow, atrial systole, protodiastole, etc., disappear. The summit of the curve is "M" shaped: the first peak represents the isometric contractions, the negative cusp is due to the forward movement of the fused pulmonary valves (piston movement) and the second peak represents the rapid ejection. The descending part of the curve is steep. The chronology of the infundibular contraction is normal and correlated to the ventricular hemodynamics.

Infundibular geometric section was found ellipsoidal: the infundibular diameters were greater in left anterior oblique projection than in the right, in every correspondent phase of the cardiac cycle. Responsible for this deformation were the hypertrophic myocardial bands (crista supraventricularis, parietal and septal band).

Simple infundibular hypertrophy can be distinguished from other infundibular conditions complicating pure valvular pulmonary stenosis (subvalvular and tunnel type) by evaluating with our method the degree of infundibular elasticity (maximum systolic diameter) and the modality of the contraction. The maximum infundibular systolic diameter was found equal to or larger than that of pulmonary valvular ring. The infundibulum was totally contracted at the beginning of diastole. The reported concept in the recent literature of "functional infundibular stenosis" (due to the premature systolic contraction of a hypertrophic infundibulum) complicating pure pulmonary valvular stenosis, cannot be accepted.

To explain the ventricular hypertension persisting after valvulotomy, the loss of infundibular elasticity due to a sclerotic process affecting a hypertrophic myocardium might be considered as an etiologic factor.

The physiopathology of the infundibular mechanics and hemodynamics are discussed. The clinical findings are correlated.

Clinical and Physiologic Evaluation of Ten Patients Subjected to Open Repair of Interventricular Septal Defects

Don W. Chapman, Houston, Tex.

The surgical procedures now employing the use of the mechanical heart have enabled successful closure of ventricular septal defects. Detailed evaluation of the clinical and physiologic characteristics of our first 10 patients will be presented. These included the repair of a ruptured septum following a myocardial infarction. On the fifth postcoronary occlusion day, the patient was thought to have spontaneously ruptured the ventricular septum, and went into predominantly rightsided cardiac failure. At the end of 9½ weeks, his heart was catheterized and the diagnosis confirmed. Shortly thereafter the 3.5 x 2 cm. hole was successfully repaired. One of the patients revealed the typical clinical findings of an associated aortic insufficiency in addition to the interventricular defect. The ventricular septal defect was characterized by a continuous to-and-fro machinery type murmur heard best in the third and fourth left parasternal interspaces. This murmur disappeared completely following surgery, but the findings of aortic insufficiency persisted. It may have been due to a sinus of Valsalva fistula with a deficient aortic valve, or inadequate support of the aortic valvular cusps.

From preliminary studies it would appear that the size of the ventricular defect constitutes the major anatomic variable, and determines the re-

sultant clinical and hemodynamic pattern. Small defects with no pulmonary hypertension and only a small amount of left-to-right shunt, may be tolerated well without surgery. Large defects with severe pulmonary hypertension, marked increase in pulmonary vascular resistance, reversible shunts, and marked right ventricular hypertrophy (electrocardiographic or x-ray evidence) may have passed the stage where closure will produce significant benefits. Those patients with mild to moderate pulmonary hypertension, mild to moderate increased pulmonary vascular resistance, predominantly left-to-right shunts, and either mixed ventricular hypertrophy or predominantly left ventricular hypertrophy, may provide the best subjects for surgery.

Mechanism of the Hypocholesterolizing Effect of the Diethanolamine Salt of the Camphoric Acid Ester of α,4-Dimethylbenzyl Alcohol

Thomas B. Clarkson, J. Stanton King, Jr., and Nelta H. Warnock, Bristol, Tenn.

In experiments using cholesterol-fed cockerels, no evidence was found for the participation of liver damage, an aperient action, choleresis, intestinal flora, or a heparin-like "clearing" effect in the inhibition by the diethanolamine salt of the mono-(+)-camphoric acid ester of α,4-dimethylbenzyl alcohol (DMA) of serum and tissue cholesterol elevations. In normal birds, serum cholesterol levels, body weight, or rate of weight gain was unaffected by DMA treatment.

The effect of DMA given orally was not enhanced by the cofeeding of adenosine-5-phosphoric acid or of a combination of betaine, folic acid, and vitamin B_{12} in a "therapeutic" type experiment, in which cholesterol feeding both preceded and accompanied drug treatment.

The actions of the chemical components of DMA, singly and in various combinations, have been examined. Apparently, the net effect is a composite of several contributions.

Cockerels were fed 1 per cent cholesterol for 10 weeks. Subsequent DMA treatment hastened the return of the serum levels to normal, and produced a favorable effect on the regression of atherosclerotic lesions, as reflected by cholesterol measurements in 4 major arteries. Aortic hexosamine was equally elevated in the 2 groups.

Investigations of Intravenous Plasmin (Fibrinolysin) in Humans: Physiologic and Clinical Effects

Eugene E. Cliffton, Malcolm Siegel, and Carlo E. Grossi, New York, N. Y.

This paper will report the results of intravenous infusion of human plasmin (fibrinolysin) in 30 patients in the years 1953 to 1956. It has been shown that this material can be injected intravenously without serious side effects other than a moderate pyrogenic reaction and slight hypotensive effect in some patients. The pyrogenic reaction has been shown to be due to the streptokinase-streptodornase used for activation of the human plasminogen. Varying doses have been used from very small amounts originally in the first 5 patients, to therapeutic doses amounting to the highest treatment dose of 8 mg./Kg. in 1 individual, and several patients have received more than 1 infusion of plasmin. Several of these patients were postoperative patients, so that a good test of the hemorrhagic effect of plasminogen was obtained and there were no serious bleeding episodes. Others were advanced carcinoma patients and postmortems were obtained in several of these to evaluate the general effect of the plasminogen.

There has been only a moderate fall in accelerator globulin, proconvertin and fibrinogen following infusion of plasmin, and this has rapidly returned to normal. The antiplasmin level of the patient has a definite effect on the in vivo lytic effect obtained. Slight change in the antiplasmin occurs during the course of the infusion, and following the infusion there is a marked increase in the antiplasmin level. Therapeutic effects have been excellent in 5 patients with thromboses; 2 with pulmonary emboli. Four patients with peripheral arterial emboli showed definite improvement in the circulation but ultimately regressed, but each of these had old, fibrotic emboli which could not possibly have been dissolved. The results, however, suggest a combined treatment of peripheral emboli with plasmin and embolectomy which should give markedly improved results. One patient with extensive arterial thrombosis of the iliac and femoral arteries was treated by local instillation of plasmin with complete lysis of thrombus and return of peripheral pulses including the dorsalis pedis. Other results will be discussed in detail.

Ivalon Tubes for By-Pass of Long Segments of Aorta

William R. Cole, James A. Helmsworth, and Louis G. Herrmann, Cincinnati, Ohio.

The suitability of Ivalon as a material for prostheses for permanent implantation has been demonstrated by earlier investigators. The success of Grindlay's experiments with this spongiform plastic suggested many possible uses. Lewis' results with tubes of this material inserted to replace arterial segments drew the attention of investigators looking for blood vessel substitutes other than biologic material.

The present report covers an investigation of the suitability of long tubes of Ivalon for shunts around the full length of the descending thoracic aorta in dogs. In these experiments the aorta was severed and the entire distal circulation was car-

ried through the plastic prosthesis which bridged from the terminal level of the aortic arch to aorta at the diaphragmatic level. The continued function of the long prostheses has been proven by survival of the animals and by angiography. A series of roentgenograms has been made showing the course of the circulation shunted by the Ivalon tube to the lower two thirds of the body.

There will be a brief discussion of the potential applications of this type of shunt around long segments of aorta. The usefulness of this kind of plastic tube as a temporary shunt to provide an alternate course for the main aortic stream during resection and replacement of segments is confirmed. The concept of this type of shunt as a permanent alternate course for the aortic stream diverted around an unresectable aneurysm will be noted.

Studies on Mixing in the Central Circulation of Man and Dog

Hadley L. Conn, Jr.,† and Donald F. Heiman, Philadelphia, Pa.

There has been considerable debate regarding the nature of blood flow and mixing in the central circulation, particularly whether the "exponential washout" theory of Newman, or the "random-walk" theory of Sheppard is most applicable. Further information on these matters is presently provided by radiopotassium dilution curve data from 10 patients and 10 dogs. Multiple radiopotassium injections were made into most components of the central circulation, and both left-heart and arterial sampling sites were used. Nearly all curves in which the lung circulation was included between injection and sampling sites (including pulmonary artery-left atrium curves in dogs), showed terminal exponential slopes which were essentially the same for all injections in the same subject. Exceptions were curves obtained by peripheral venous injections which frequently showed flatter, exponential, terminal components. The results from these subtects are compatible with the ideas (1) that "random-walk" (laminar) mixing occurs from peripheral vein to right ventricle, but that a different pattern of mixing, consistent with the "exponential washout" but not the random-walk concept, occurs in most of the remaining central circulation, (2) that the pulmonary mixing bed, normally about 500 ml. in man, is the main volume determinant of the dilution curve slope; (3) that the slope method of determining pulmonary mixing volume may be inaccurate with peripheral injections because of failure of indicator to enter the right ventricle in one filling cycle.

In 2 patients with severe mitral, and 1 with severe tricuspid insufficiency, analysis of the multiple curves showed that the left heart and right heart volumes, respectively, were the volume determinants of the terminal slope of vein-to-artery curves. The final conclusion then, is that, providing indicator is delivered nearly instantaneously to the right heart, the main volume factor governing terminal slope is the largest mixing component existing, regardless of location, between injection and sampling sites.

Simultaneous Angiocardiographic and Isotope Dilution Studies: With Special Reference to Physical Properties of Radio-opaque Media and to Opacification Pattern in Patients with Mitral Heart Disease

Hadley L. Conn,† Claude R. Joyner, Donald F. Heiman, and Harry F. Zinsser, Philadelphia, Pa.

Angiocardiography provides a method for obtaining differential circulation times within the various cardiac chambers and great vessels. Plots of apparent density against time yield interesting opacification patterns, particularly in mitral stenosis where left atrial density increases relative to left ventricular density as opposed to practically equal density in normals. To understand and interpret such patterns requires further knowledge relative to the physiologic circulatory effects, physical characteristics, and mixing behaviour of radio-opaque media following rapid intravenous injections.

To study these factors, we obtained isotope dilution curves following intravenous injections of 45 ml. physiologic saline containing K^{42} and 45 ml. iodopyracet labelled with I^{131} into 10 patients (7 with mitral disease and 3 without heart disease). Curve slope, cardiac output, mean circulation time, and central blood volume were determined for both saline-isotope and iodopyracet-isotope injections. Also relative circulatory transmission rates were determined for K^{42} and I^{131} simultaneously injected with 45 ml. iodopyracet. Isotope curve contours were correlated with left heart angiocardiographic patterns.

Cardiac outputs were increased, but no significant difference was demonstrable between the outputs calculated from saline-isotope and those calculated from iodopyracet-isotope injections. In comparison with saline curves, 6 iodopyracet curves were delayed, 2 were faster and 2 were unchanged. These differences may be due to the fact that saline can be injected more rapidly than equal quantities of iodopyracet. During angiocardiography, simultaneously injected K^{42} and I^{131} reached the arterial blood in equal amounts (relative to amount injected) up to the time of recirculation. Isotope curves correlated well with duration of left heart opacification but not with the differential opacification of left atrium and ventricle as observed in patients with mitral stenosis. The study did not provide evidence of any effect attributable to the differences in the physical properties of the 2 solutions or indicators.

Control of Oral Anticoagulant Therapy with a Standardized Clotting Time

W. Ford Connell and George A. Mayer, Kingston, Ontario, Canada.

A highly reproducible standardized clotting time (SCT) has been used by the authors for 2½ years for the control of oral anticoagulant therapy, in 245 cardiovascular patients for a total of 12,350 treatment days. The Quick 1-stage prothrombin test (PTR) was used for comparison in the first 1 5 of these patients. Various coumarin derivatives and coumarin-like drugs (bishydroxycoumarin, ethyl biscoumacetate, acenocoumarin and phenindone) were utilized during the course of this study.

Significant and consistent elevation of SCT was produced by all the drugs used. The time required to achieve an adequate SCT prolongation averaged 4 days or longer for all 4 drugs studied. This was an unexpected finding, fully justifying in our opinion our initial use of heparin to initiate the therapy in most cases.

No significant correlation was found between the 2 tests. Adequate SCT prolongation was noted at widely varying levels of PTR.

No difficulty was experienced in maintaining adequate SCT prolongation in 80 per cent of total treatment days.

When the SCT was within our therapeutic range, no hemorrhagic accidents or thromboembolic complications were observed. The PTR gave us poor warning of such complications.

The data presented demonstrate that the SCT as used by us is distinctly superior to the Quick 1-stage prothrombin test for the control of oral anticoagulant therapy. In fact, during the past 8 months we have treated 70 patients, for 1,177 treatment days, carrying out the standardized clotting time alone with excellent clinical results.

Syndrome of Truncus Arteriosus Communis with Large Pulmonary Flow: Resemblance to Patent Ductus Arteriosus

Stephen Contro, Robert A. Miller, Harvey A. White, and Willis J. Potts, Chicago, Ill.

The clinical picture of patency of the ductus arteriosus is well established. Since surgical correction of this condition became practical it became evident that other cardiac anomalies may mimic the clinical features of the patent ductus. In 400 children, coming to surgery at the Children's Memorial Hospital, with a diagnosis of patent ductus, a common arterial trunk was found in 4 instances. All 4 patients were acyanotic at rest and on exercise, and had a murmur localized to the second and third left interspaces parasternally. In 3 of the patients this murmur had a rather rumbling quality and extended through systole and well into, but not through, diastole. Although the examiner noted that the murmur was "rather atypical" for a patent ductus, it was made clear that this was not the familiar soft continuous bruit commonly heard in patients with truncus and dilated bronchial arteries. The fourth patient had a murmur in systole only, with a sharp pulmonary second sound.

The x-ray in all 4 patients showed a large heart, a prominent pulmonary artery segment and increased pulmonary vascular markings. The electrocardiogram showed left heart strain in 1 case, combined heart strain in 2, and right heart strain in the fourth, which was thought to be a ductus with pulmonary hypertension.

Since all were considered "atypical ductus," a retrograde arteriogram was done in all 4 cases, consistently revealing injection of the pulmonary vessels from the aorta.

Cardiac catheterization in 1 child showed a large left-to right shunt, and a small right-to-left shunt at the level of the "pulmonary artery." The catheter was passed from "pulmonary artery" to descending aorta. These observations serve to emphasize the hemodynamic similarity among patent ductus arteriosus, truncus arteriosus with large pulmonary flow, and aortic septal defect.

Bronchial Obstruction due to Anomalies of the Pulmonary Arteries

Stephen Contro, Robert A. Miller, and Willis J. Potts, Chicago, Ill.

The group of anomalies caused by deranged development of the primitive aortic arches, often referred to as "vascular rings," have become familiar clinical entities, since their surgical correction has become possible. Until the recent case, reported by 1 of the authors, however, it has not been generally recognized that severe, even fatal obstruction of the trachea and bronchi may be caused by congenital anomalies of the pulmonary arteries.

Three cases will be presented in which an anomalous left pulmonary artery encircled the origin of the right main bronchus and the lower end of the trachea so tightly as to produce collapse of these structures and marked respiratory dysfunction. Another case will be presented in which huge congenital aneurysms of the right and left pulmonary arteries caused fatal compression of both main stem bronchi. These cases afford an opportunity to emphasize the peculiar embryology of the pulmonary arteries.

Since surgical correction of these pulmonary artery anomalies is feasible, it is suggested that such cases be included in the differential diagnosis of the "vascular ring" type of respiratory obstruction of the newborn.

Effect of Cardiac Arrhythmias on Coronary Flow

Eliot Corday, Beverly Hills, Calif., Lauro B. de Vera, Los Angeles, Calif., Herbert Gold, Beverly Hills, Calif., and Teja Gerth, Los Angeles, Calif.

It is well recognized that cardiac arrhythmias can precipitate coronary insufficiency, yet their effect on the coronary flow has so far not been accurately measured. In view of this, the authors have conducted experiments in the dog, pig and in the human to evaluate the coronary flow in cardiac arrhythmias.

In the dog's beating heart, the antegrade and retrograde (collateral) flows of the cannulated anterior descending artery were measured simultaneously during arrhythmias. These arrhythmias either occurred spontaneously or were induced by stroking or application of aconitine. In 25 dogs, it was noted that premature atrial and ventricular systoles reduced the antegrade coronary flow, on the average, by 15 per cent (4.7 ml.); paroxysmal atrial flutter, 22 per cent (6.8 ml.); paroxysmal atrial tachycardia, 35 per cent (11 ml.) and ventricular tachycardia by 60 per cent (18.7 ml.). The collateral flow was also reduced proportionately to the antegrade flow.

Making use of the finding that the arrhythmias produce an apparent parallel effect on the systemic blood pressure and coronary flow, brachial arterial pressure tracings were then recorded in selected human subjects. Clinically, the same pattern of systemic pressure drop was noted as in the animal. By correlation of pressure values, the theoretic estimate of human coronary flow reduction was then made.

The authors conclude that the cardiac arrhythmias have a deleterious effect on the coronary flow and should be treated promptly in the patient with coronary artery disease.

Abnormal Pulmonary Function in Heart Failure: A Comparison of Hypertensive and Rheumatic Heart Disease

Richard S. Cosby, Ellery C. Stowell Jr., Ray Hartwig, and Mary Mayo, Los Angeles, Calif.

Eight patients with hypertensive heart disease with congestive failure, 14 patients with rheumatic heart disease, mitral stenosis and congestive failure, and 16 patients with pulmonary disease with emphysema and right heart failure were subjected to pulmonary function evaluation. All patients, bedridden at the time of examination, were moderately or severely dyspneic. Lung volume studies were obtained. Analyses of distribution and diffusion were performed with Riley's technics. Arterial oxygen saturations following positive pressure breathing, exercise and 100 per cent oxygen were obtained. Expiratory flow patterns were analyzed by recording pneumotachograms simultaneously with single breath curves by an infrared analyzer or a mass spectrometer. The results showed a distinctive though not diagnostic pattern of respiratory abnormality in hypertensive heart disease with cardiac asthma. There was a considerable reduction in vital capacity and in those indices denoting obstructive ventilatory insufficiency. Of greatest significance in ventilatory measurements was the ratio of breathing reserve to maximum breathing capacity. A moderate degree of CO_2 retention was present with diminished alveolar and arterial oxygen tensions. The aeration gradient was markedly, and the transfer gradient minimally, increased. In spite of low vital capacities, relatively little arterial oxygen desaturation was present. Minimal increases in per cent venous admixture and practically no diminution in oxygen diffusing capacity were present. In patients with rheumatic heart disease in congestive failure at comparable levels of disability, vital capacities were greater, bronchospastic features were absent, CO_2 retention was rare and abnormalities of diffusion constituted the chief abnormality related to the transfer gradient.

Finally the precise nature of bronchospastic respiration in hypertensive heart disease was investigated by correlation with arterial pCO_2 and pulmonary artery pressure. Bronchospastic respiration appears to be a positive pressure device to insure adequate alveolar ventilation and arterial oxygen saturation in hypertensive cardiac failure.

Variable Sensitivities of Rhesus Monkeys to a High-Fat, High-Cholesterol Diet

George E. Cox, Betty J. Hall-Taylor, Laverne G. Nelson, and C. Bruce Taylor, Chicago, Ill.

Hypercholesterolemia up to 670 mg. per cent has been induced in young adult male and female rhesus monkeys ingesting ad libitum an adequate diet containing 20 per cent fat with 1.5 per cent cholesterol (by weight). To date, 21 monkeys have received high cholesterol diets for periods up to 2 years. Control serum cholesterol levels averaged 154 mg. per cent (±30 mg. per cent). Responses to some earlier high cholesterol dietary regimens were only moderate: of 11 animals fed for 1 to 12 months, only 2 exceeded serum cholesterol levels of 300 mg. per cent (Circulation **10:** 1, 1954). Currently we are using a stock diet consisting of commercial monkey food supplemented with ascorbic acid, folic acid and pyridoxine. Butter and cholesterol are added to the experimental diet to attain proportions of fat stated above. Animals ingesting the present experimental diet show a progressive weight gain and have apparent good health. Responses to our current high cholesterol diet have been more rapid and greater. Eleven of 15 animals have shown serum cholesterol levels exceeding 300 mg. per cent after experimental feeding periods of 1 week

to 7 months (median period of 2 months). Prolonged cholesterol feeding demonstrated 3 types of responses somewhat comparable to those of man: (1) Highly sensitive (6 animals) with levels between 502 and 670 mg. per cent; (2) intermediate (5 animals) with levels between 335 and 423 mg. per cent; and (3) resistant (4 animals) with levels between 185 and 274 mg. per cent. The similarity of these responses to those of humans will be discussed with reference to the potential value of the monkey in experimental studies of factors concerned in human atherosclerosis. Other comparative data on hepatic cholesterol concentration and in vitro synthesis of liver biopsies from monkeys and humans will also be discussed.

Congenital Aorticopulmonary Septal Window: Physiologic and Surgical Considerations

Cecil M. Couves, Denton A. Cooley, Joseph R. Latson, and Dan D. McNamara, Houston, Tex.

Congenital defects in the cardiac partition may be located in the interatrial, interventricular, or aorticopulmonary septum. Differentiation of the lesion may be made by careful diagnostic studies including electrocardiography, cardiac catheterization, dye dilution curves, and angiocardiography. Criteria for selection of patients with aorticopulmonary septal defect for surgical correction are based upon the degree of pulmonary vascular resistance present since a high resistance in the pulmonary system may lead to a fatal outcome from closure of the shunt.

Before the use of hypothermia or cardiac by-pass in the surgical repair of this lesion, serious hemorrhage often resulted from an attempt to divide or ligate the tense friable structure.

In 2 patients age 4 and 14 years with large aorticopulmonary septal windows measuring 2.5 and 3.5 cm. in diameter, respectively, the aorticopulmonary communication was divided successfully using general body hypothermia in the younger patient and temporary extracorporeal circulation in the older.

At present with the application of hypothermia and the cardiac by-pass, even large pulmonary septal defects may be repaired with relative safety.

Pathogenesis of Experimental Hypertension Produced by Carotid Sinus Area Constriction in Dogs

Earle E. Crandall and George E. Wakerlin, Chicago, Ill.

Previously, our research group reported that bilateral constriction of the carotid sinus area, including the internal carotid and external carotid (and occipital) arteries, in the dog resulted in hypertensions of 30–100 mm. Hg in 9 of 10 dogs (Circulation Research, **2:** 416, 1954). Presently, these hypertensions have durations of 23–36 months and have been confirmed in 3 additional dogs. General health, appetite, body weight, body temperature, urinalyses and heart rate have continued normal. Passive transfer of homologous antirenin to hog renin was without antihypertensive effect. Results with sodium cyanide suggested absent carotid body function. Phenoxybenzamine produced an acute reduction in pressure to normotension. Chronic treatment with phenoxybenzamine for 4 months showed significant reduction in pressure. Cerebral angiography suggested that the hypertension is compatible with a grossly normal cerebral arterial tree. Bilateral constriction of the vertebral arteries in 6 dogs resulted in normotension in 4, a questionable hypertension of 16 mm. Hg in 1, and a hypertension of 40 mm. Hg in 1. Bilateral constriction of the internal and external carotid (and occipital) arteries above the sinus in 3 dogs produced hypertension, as did bilateral constriction of the denervated sinus in 2 dogs. Five dogs subjected to bilateral removal of the carotid sinus developed modest hypertensions averaging 30 mm. Hg. These preliminary findings suggest that pathogenesis involves an alteration in cerebral hemodynamics (decreased cerebrovascular pulse volume?) with both increased vasoconstrictor tonus and a humoral pressor factor.

Clinical Grading of the Severity of Obliterative Arterial Disease of the Lower Extremities: II. Clinical and Laboratory Correlations

John J. Cranley and Raymond J. Krause, Cincinnati, Ohio

The degree of arterial insufficiency existing in extremities with obliterative arterial disease may be estimated as follows: grade I, a decrease in amplitude of the dorsalis pedis and posterior tibial pulse (the diagnosis having been established by a history of intermittent claudication); grade II, absence of the dorsalis pedis and posterior tibial pulse; grade III, absence of the popliteal pulse, or absence of the dorsalis pedis and posterior tibial pulse in a diabetic patient; grade IV, rest pain in the foot and/or rubor of the foot on pendency; and grade V, continuous pain in the foot, petechial hemorrhages of the dorsum of the foot, or skin necrosis.

The incidence of each grade in 343 extremities with obliterative arterial disease was: grade I, 56 (16 per cent); grade II, 48 (14 per cent); grade III, 132 (39 per cent); grade IV, 77 (22 per cent); grade V, 30 (9 per cent). The amputation rate during an observation period of 6 to 48 months, and the average time from initial observation to amputation was as follows: grade I, 0; grade II, 1 (2 per cent) in 18 months; grade III, 7 (5 per cent) in 12 months; grade IV, 16 (21 per cent) in 9 months; and grade V, 13 (43 per cent) in 4 months.

The effect of 50 mg. of azapetine phosphate intravenously, reflex vasodilatation by means of a steam tent, and tibial nerve block on the toe temperature and digital pulse in 14 normal and 41 extremities in the first 4 grades of arterial insufficiency was studied. Correlation between the severity of the disease as judged by clinical examination, and response of skin temperature to the various methods of producing vasodilatation was good. All of these methods were effective in elevating the skin temperature of the toe in grade I and II extremities, and were relatively ineffective in grade IV extremities. In grade III extremities, the response to azapetine phosphate was minimal, but the response to reflex vasodilatation and tibial nerve block was appreciable.

Observations on the Use of a Rotating Disc Reservoir Oxygenator in Open Intracardiac Surgery

Frederick S. Cross, Robert M. Berne, Henry A. Zimmerman, and Earle B. Kay, Cleveland, Ohio

Direct vision intracardiac surgery, utilizing a heart-lung apparatus, has become an accepted surgical technic, especially in certain congenital lesions. The present report is based on clinical experience with a simple and adequate rotating disc reservoir-oxygenator. This experience includes the repair of valvular pulmonic stenosis, infundibular pulmonic stenosis, atrial septal defects, and ventricular septal defects, occurring as isolated lesions or in various combinations.

Seventeen cases have been operated on to date (April 2, 1956). Cardiac by-pass periods ranged from 12 to 44 min., with flow rates of 40 to 80 ml./Kg./min. in patients weighing from 24 to 59 pounds. The pump-oxygenator has functioned smoothly and efficiently allowing the surgeon to give full detail to the operative procedure and to operate in an unhurried and precise manner.

Complete physiologic studies have been carried out on each patient. There has been no significant change in the red cell and white cell counts, hemoglobin, and hematocrit. The clotting mechanism has been undisturbed. Platelet counts done by phase microscopy following cardiac by-pass were about one-half their preoperative values, except in 1 instance when the count was 92,000. The other platelet counts postoperatively were all above 130,000. Likewise, there was no significant change in plasma fibrinogen and clot lysis. Clotting time was readily brought to normal postoperatively with protamine sulfate in doses calculated at one-half the total heparin dosage. There were no cases of postoperative bleeding.

Utilizing 1.5 to 2.5 per cent carbon dioxide in oxygen in the oxygenator, no serious acid-base problems were encountered. Blood pH during the run ranged from 7.14 to 7.62, the majority being between 7.3 and 7.4. There has been some evidence of a mild metabolic acidosis developing during the by-pass period, which quickly corrects itself postoperatively. The cause of this metabolic acidosis is being investigated at the present time.

In the first 17 cases there were 3 deaths, with only 1 death occurring in the last 11 cases. There have been no deaths attributable to the pump-oxygenator per se. One death was operative, 1 postoperative due to pulmonary complications, and the third was also postoperative due to multiple intracardiac defects incompletely corrected.

A distinct advantage of direct vision intracardiac surgery in our experience to date has been the finding of other intracardiac defects completely missed in the preoperative workup and which would have been missed by the usual closed surgical technics. In addition, it has been the impression to date that the various intracardiac defects can be corrected better and with less over-all trauma and danger to the patient, than with the previously utilized closed technics.

Coarctation of the Aorta and Pregnancy: A Report of Nine Cases with Twenty-one Pregnancies

James H. Currens, W. Raymond Shanahan, and Seymour L. Romney, Boston, Mass.

In the past 25 years pregnancy and coarctation of the aorta have been observed in 9 patients at the Boston Lying-In Hospital. A study of the clinic blood pressure recordings in 13 pregnancies revealed the following: (1) the blood pressure remained the same during pregnancy 10 times; (2) the blood pressure declined during pregnancy in 2 patients; and (3) the blood pressure rose in the last trimester of pregnancy in 1 patient. There have been 21 successful pregnancies in these 9 patients.

The blood pressure was determined 6 weeks postpartum under similar conditions in 11 pregnancies (8 patients). The blood pressure was elevated by 10 to 60 mm. (systolic and diastolic) above any of the readings during pregnancy after 4 pregnancies and was in the same range after 7 pregnancies.

Fourteen pregnancies were terminated by normal pelvic delivery while 7 caesarian sections were performed (3 for pelvic disproportion). Corrective surgery for coarctation was successful in 2 patients when not pregnant and there has been 1 subsequent, uncomplicated pregnancy with normotension. There were no maternal or fetal deaths in these patients.

A review of the literature regarding coarctation of the aorta and pregnancy reveals 105 patients with 11 recorded deaths due to rupture of the aorta in 7 cases. In only 1 case did rupture occur during labor.

The absence of toxemia was conspicuous in the 21 pregnancies and proteinuria of more than slight degree was not recorded in any of these pregnancies. The recorded cases in the literature are consistent with these observations. This sugges

that aortic constriction and the related diminution of pulsatile pressure to the abdominal or pelvic organs (i.e., kidney, adrenal, uterus) may be a protective mechanism against pregnancy toxemia.

Transient Bundle-Branch Block in Coronary Artery Disease

Milton Cutler, Hammonton, N. J.

Bundle-branch block once established has been considered to be permanent. Instances showing return to normal conduction have been reported. Transient bundle-branch block in apparently normal individuals and secondary to heart disease has also been reported. Alternating block has been illustrated. That block may be influenced physiologically by varying heart rates, stimulating doses of atropine, aminophylline, controlled breathing, has been demonstrated.

During the first week following an attack of coronary thrombosis in a 50-year-old woman, it was noted that the left bundle-branch block which had developed following the attack reverted to normal rhythm during various phases of the respiratory cycle, irrespective of heart rate. It was then noted that block could be changed to normal conduction by the simple expedient of holding the breath in deep inspiration. This reverted to bundle-branch block again on expiration; on a few occasions when it did not revert to block, this was accomplished by making the patient hold the breath in deep expiration. Later on however, it was seen that expiration or inspiration could change block to normal conduction and vice versa. After a few weeks, the block became more difficult to convert and in spite of drugs and respiratory exercise became permanent. Slides showing transition during the electrocardiogram are shown.

In another case of transient bundle-branch block immediately following coronary thrombosis, there was an eventual recovery of normal conduction. Here too block was converted to normal conduction by deep inspiration. Slides showing transition are also shown.

Two other cases of transient bundle-branch block in coronary artery disease are illustrated. Various explanations are offered for this block following thrombosis: edema encroaching the bundle, involvements of part of the bundle fibers with apparent freedom of other fibers, anoxia of the bundle, alternate conduction routes, fatigue of the bundle, metabolic influence, all with the additional influences of vagal reflexes.

Mitral Insufficiency: Preparation of Experimental Animals for Study of Acute and Chronic Sequelae

Julio C. Davila, Domingos J. Morais, Page Acree, Thomas Richardt, A. Jane Fritz, and Robert P. Glover, Philadelphia, Pa.

The production of valvular lesions of the heart in experimental animals, which will permit the study of the pathologic physiology of the chronic state, has been attempted by numerous investigators. Mitral regurgitation has been produced in animals by many methods, any of which will permit the study of the acute changes. However, significant mitral insufficiency is invariably fatal within a very short time.

Several technics for producing variable, and to some extent controlled, degrees of mitral regurgitation have been used in this laboratory in 78 dogs over the past 2 years. In the initial phases of this study our experience was that of all other investigators in this subject. Although acute studies were very satisfactory, all animals in which significant degrees of regurgitation were produced died within a few minutes to less than 1 month after operation. At autopsy, these animals showed the changes of massive acute congestive failure. Animals in which lesser degrees of regurgitation were obtained often survived for indefinite periods of time, during which the murmur gradually disappeared. When these were sacrificed, or reoperated as long as 6 months later, no significant cardiovascular changes were found. Examination of the valve revealed healing which took several forms and was associated with regained competence.

Approximately 1 year ago it was decided to ligate the inferior vena cava below the renal veins at the same time that mitral regurgitation was produced. This resulted in a survival of over half of the animals so prepared. The current survival rate is even higher. This is so despite the fact that very substantial degrees of regurgitation are produced. The animals which have now been followed for 8 to 10 months have persistent loud murmurs, show evidence of cardiac enlargement and progressive increase in left atrial pressure.

In 78 dogs studied mitral regurgitation was produced by several methods but without vena cava ligation in the first 37. Vena cava ligation was added in the last 41 animals. Of the original 37 animals, 19 died within 3 weeks, some within a few minutes, most of them within 3 or 4 days. The survivors (18) were observed for as long as 6 months. None had significant mitral regurgitation. Of the 41 animals in which the vena cava was ligated, 20 have survived 2 to 10 months. These animals have persisting, loud murmurs, and in those which have been studied subsequently there is evidence of cardiac enlargement and of progressive increase in left atrial pressure.

The feasibility of producing mitral regurgitation in experimental animals with chronic survival and evidence of pathologic sequelae, makes possible more extensive, better controlled, and more practical study of the pathologic physiology of this condition.

Cardiac Fibrinoid Lesions in Rabbits

Richard L. Davis, Joel G. Brunson, and Peter E. Fehr, Minneapolis, Minn.

The effects produced in rabbits by carotid-jugular cross circulation or temporary carotid-jugular

shunts, alone or in combination with meningococcal endotoxin, sodium polyanethol sulfonate (Liquoid), cortisone, and colloidal iron or thorium dioxide were studied. Two hundred ninety-nine rabbits were used in the experiments.

About 60 per cent of 33 animals subjected to the shunting procedures alone showed the presence of extensive myocardial and valvular alterations consisting of cellular reaction, hemorrhage, and muscle necrosis. Approximately 40 per cent also had extensive deposits of fibrinoid in the walls of the coronary arteries and within the heart valves. No structural changes were observed in other organs. There was a marked decrease in incidence of cardiac fibrinoid lesions when excessive quantities of heparin were used as anticoagulant.

When endotoxin, Liquoid, cortisone, or 1 of the colloidal compounds was given in conjunction with the shunting procedures, fibrinoid lesions of the kidneys, lungs, spleen, and liver were present in addition to the cardiac lesions. These lesions were morphologically similar to those observed when any of these substances was given in conjunction with an intravenous injection of endotoxin. In those animals given colloidal iron or thorium dioxide with the shunting procedure, these materials were admixed with the fibrinoid in the lesions. Appropriate controls showed no significant lesions.

The results of these experiments indicate that isolated cardiac lesions with fibrinoid deposition in the arteries and valves can be produced regularly by the cross circulation or temporary arteriovenous shunt procedures. Since diffuse fibrinoid lesions were observed when a shunting technic was used in conjunction with 1 of the above mentioned materials, and since similar lesions are produced when these same materials are used in association with endotoxin, it is suggested that the shunting technics and endotoxin act similarly. These experimental results support the previously stated hypothesis of the derivation from the blood of fibrinoid or its precursors.

Prevalence and Incidence of Coronary Heart Disease in the Framingham Study

Thomas R. Dawber, Framingham, Mass., George V. Mann,† Framingham, Mass., and Felix E. Moore, Bethesda, Md.

A study has been made of the amount of coronary heart disease found at the initial examination of the Framingham Study and of the subsequent development of new disease during the next 4 years. The population studied consisted in the beginning of 4,494 randomly selected persons between the ages of 30–60. As many of these persons as possible were observed by examinations at 2-year intervals and/or by information from other sources, e.g., hospitalizations or records of private physicians. The examination consisted of a standardized, comprehensive history of cardiovascular disease together with physical examination of the cardiovascular system, chest x-ray, electrocardiogram and laboratory studies. Coronary heart disease was defined as either the development of unequivocal clinical and/or laboratory signs of myocardial infarction and/or the appearance of typical symptoms of angina pectoris. Persons in whom the diagnosis of either myocardial infarction or angina pectoris were possible but not definite were classed as possible myocardial infarction or angina pectoris.

The prevalence of myocardial infarction at the initial examination showed a progressive increase with age in males. The most notable increase occurred after age 50. The presence of this disease was almost nonexistent in females. Angina pectoris and evidence of myocardial infarction were almost equally prevalent in males. Angina pectoris increased progressively in both males and females in a similar degree. There is a relatively large group of people in both sexes in whom a diagnosis of possible myocardial infarction or angina pectoris is made. These represent almost two thirds of all persons in whom a diagnosis of coronary heart disease seems indicated.

The incidence of angina pectoris also increased progressively with age and was similar in the 2 sexes. The incidence of myocardial infarction in males was approximately 3 times that of females for these age groups. The incidence of coronary heart disease over a 2-year period was of similar magnitude to the prevalence observed at the beginning of the study.

Bacterial Endocarditis Following Cardiac Surgery

Clarence Denton, Elias G. Pappas, Joseph Uricchio, Harry Goldberg, and William Likoff, Philadelphia, Pa.

One of the risks following cardiac surgery is the development of bacterial endocarditis. A total of 2,263 patients operated in the interval between 1950 and 1955 was reviewed to determine the incidence, etiology, clinical manifestations and mortality of this complication.

Twenty-two instances of bacterial endocarditis were discovered. Two occurred among 374 patients with congenital heart disease (0.5 per cent), and 20 in the 1,889 cases requiring valve surgery (1 per cent).

In 11 of the patients with rheumatic endocarditis, the aortic valve alone was involved. Six of the patients had mitral valve disease, and 4 had combined mitral and aortic lesions. Extensive calcification of the valve was observed in 12.

One-third of the infections occurred within 10 days of surgery, and an equal number more than 3 months later. The remainder were recognized at an intermediate time.

The most common offending organism was the coagulase negative *Staphylococcus aureus* which was most resistant to penicillin therapy. Only 8 patients recovered of the 16 treated vigorously.

Clinically and bacteriologically, bacterial endocarditis occurring after cardiac surgery is a more malignant lesion than commonly encountered. This probably is a reflection of the trauma to the valve, and the nature of the organism involved.

Hemodynamic Changes Following Mitral Commissurotomy

Janet Dickens and Harry Goldberg, Philadelphia, Pa.

The hemodynamics of mitral stenosis studied by simultaneous catheterization of the left and right heart have been reported previously (Circulation 12: 713, 1955). Forty-eight patients have been studied by this method. Sixteen have been reevaluated 12 days to 4 months post mitral commissurotomy.

Postoperative results were considered good in 10 patients based upon a significant increase in mitral valve flow accompanied by a significant decrease in pressure gradient. The functional mitral valve area increased in all. Although the left atrial pressure decreased generally, the good postoperative response was not always reflected by a fall in the pulmonary artery pressure.

In 1 case the flow increased markedly with no change in pressure gradient with an increase in valve area. In another, both flow and gradient fell with little or no change in valve area. A poor response was indicated in 3 patients showing little or no change in flow or gradient. In 1, the preoperative data was inadequate, but postoperatively there was a small gradient with an adequate orifice size.

The degree of mitral obstruction was not necessarily reflected by the level of pulmonary artery pressure, hypertension being present at all orifice sizes. Pulmonary hypertension may not be the sole determining factor of the severity of stenosis or requirement of surgery when direct measurements of gradient and flow across the valve are known. Although, in general, the pulmonary artery pressure fell in the presence of a good result based upon gradient and flow, the response of the pulmonary pressure was not always a reliable index of success or failure of commissurotomy.

These studies indicate that estimation of the degree of mitral stenosis and type of response following surgery cannot always be made by indirect studies of the pulmonary circulation and cardiac output obtained by right heart catheterization. The importance of simultaneous estimation of the pressure gradient and flow is emphasized.

Left Ventricular Volume in Normal Man and Alterations with Disease

Harold T. Dodge and Herbert L. Tanenbaum, Bethesda, Md.

Evaluation of left ventricular function by manometric methods depends upon demonstrating an elevated left ventricular filling pressure for evidence of left ventricular disease. Experimental animal work has indicated that an early sign of left ventricular weakness is increased left ventricular end-diastolic volume and that left ventricular pressure-volume relationships during end-diastole are such that considerably increased volumes may occur with small pressure changes until the ventricular volume becomes large. How this limits the usefulness of left ventricular filling pressure as a sensitive index of left ventricular disease in man is unknown.

Left ventricular end-diastolic volumes in man were calculated from biplane angiocardiograms. Biplane x-ray studies in which the left ventricles of 5 postmortem hearts were injected with known volumes of contrast media provides the basis for the in vivo quantitation of left ventricular end-diastolic volumes by this method.

Left ventricular end-diastolic volume has been determined in 21 patients. In 11 normal subjects or subjects with no clinical cause for left ventricular enlargement, left ventricular volumes were 60 to 131 ml. In 10 subjects with either aortic valve disease, hypertension or myocarditis, left ventricular volume were 96 to 295 ml. Of the latter group, 4 were essentially asymptomatic and had left ventricular volumes of 96 to 133 ml.; 3 were symptomatic, had normal resting pulmonary "capillary" pressures, but an increased left ventricular end-diastolic volume (169–250 ml.); and 3 were symptomatic with elevated resting pulmonary "capillary" pressures, and had greatly increased left ventricular end-diastolic volumes (274–295 ml.).

These studies indicate that the resting pulmonary "capillary" pressure is not a sensitive measure of increased left ventricular volume and therefore not a sensitive index of left ventricular disease. This might be a consequence of the normal pressure-volume relationships of the left ventricle of man, or because the elastic properties of the left ventricle during diastole are altered by disease.

Fluid and Electrolyte Disturbances Following Mitral Valve Surgery

George L. Donnelly, Colin A. Munroe, James E. Gibbons, and Edward S. Orgain, Durham, N. C.

Patients undergoing mitral valve surgery may develop metabolic changes in the early postoperative period. These include oliguria, water retention, hyponatremia, hypochloremia, and nitrogen retention. Variable changes in blood potassium and CO_2 combining power occur. This syndrome may be precipitated by fluid administration and deserves further emphasis since it can be partially or completely prevented by fluid restriction. Once fully developed it is treated with difficulty.

Of 25 consecutive patients submitted to commissurotomy 13 patients have been analyzed in detail with particular reference to fluid balance and repeated blood chemistries. Three patients developed

hyponatremia to levels of less than 130 mEq./L., accompanied by hypochloremia of less than 85 mEq./L., and rises in serum potassium to levels above 5.7 mEq./L. In 2 patients blood nonprotein nitrogen rose above 58 mg. per cent. Carbon dioxide combining power revealed minor variations, rising in 2 patients and falling in 1. One patient in whom hyponatremia proved refractory to treatment, succumbed; the remaining 2 patients reverted to normal following treatment by fluid restriction and/or the administration of alcohol. Alcohol administered orally to inhibit pituitary antidiuretic hormone, has been valuable in promoting water excretion in at least 2 of 4 patients who received it. Five additional patients developed hyponatremia in the range of 130 to 135 mEq./L. and hypochloremia to levels of 85 to 95 mEq./L., but unaccompanied by significant changes in potassium, nitrogen or CO_2 combining power. The details of these cases will be submitted, pathogenesis discussed and emphasis given to the prevention and treatment of this syndrome by fluid restriction and the use of alcohol therapeutically.

A Critical Evaluation of Drug Therapy in Hypertension

John D. Dorsett, Chapel Hill, N. C., James W. Woods, Chapel Hill, N. C., Kerr L. White, Chapel Hill, N. C., Harry Smith, Jr., Cincinnati, Ohio, and Reuben Hill, Chapel Hill, N. C.

A rigidly selected group of 16 white patients with moderately severe essential hypertension, ages 30 to 55 years, and equally divided between the sexes, was studied. Patients with overt psychological disturbances, primary renal disease, or other significant unrelated diseases were excluded. A double-blind technic was utilized to assess the effect of 3 hypotensive regimens: phenobarbital (30 mg. q.i.d.), reserpine (0.25 mg. q.i.d.) and reserpine-hydralazine combination (0.25 mg. of reserpine and 100 mg. of hydralazine q.i.d.). Drugs and placebos were contained in capsules of identical appearance and taste. Patients were classified initially by systolic and diastolic blood pressures and by social stress indices. The sociologist determined the latter by means of questionnaires and interviews. These scores were utilized to divide the patients into 4 groups of 4, balancing out the effects of these initial classifications. Patients within a group were assigned to treatments at random by the biostatistician. Patients were seen weekly for 32 weeks, and received placebo for 8 weeks, treatment for 16 weeks, and placebo again for 8 weeks, except for 4 patients who received placebo throughout. Blood pressures were taken under standardized conditions by a carefully trained nurse who was unaware of the treatment given. Clinical examinations were made by an investigator who was unaware of both treatment involved and blood pressures. Optic fundi were examined at intervals by an ophthalmologist. Laboratory measurements were made prior to and at the conclusion of the study.

Most patients showed symptomatic improvement during the placebo period. No significant blood pressure changes occurred in patients receiving placebo and phenobarbital. However, 2 who received the latter developed malignant hypertension and were dropped from the study. Patients on reserpine showed a slight decrease in pressure during treatment. The reserpine-hydralazine combination produced a significant decrease in blood pressure throughout treatment.

Clinical Application of a New Blood Pump

John E. Doyle, Arthur E. MacNeill, Roland Anthone, and Sidney Anthone, Buffalo, N. Y.

A blood pump of unique design, developed by one of us (A.E.M.), and recently modified with new plastic materials, has now been used clinically.

The blood pump is powered by a small, electrically driven piston which applies alternating positive and negative pressure with each stroke to the air chamber of the pump. The pressure is then transmitted through a sterile fluid medium to the blood chamber of the pump. This blood chamber, a straight flat, patent tube of vinyl, is divided into inlet valve, pumping chamber, and exit valve *areas*. The pressure strikes the inlet valve first, occluding it. A delay mechanism then transfers the pressure to the pumping chamber. The inlet valve, already occluded, prevents backflow from the pumping chamber.

A *constant* pressure is applied to the exit valve. The pressure within the pumping chamber is sufficient to overcome the pressure on the exit valve and after the pumping chamber empties the exit valve pressure prevents backflow.

Clinical experience with the pump has been accumulated in 16 patients in whom dialysis or ultrafiltration has been performed. Heparinized blood in the vein to vein circuit was propelled at 60 to 900 ml./min. (mean:300) for 6- to 9-hour periods.

Plasma hemoglobin determinations demonstrated a slow increase from less than 1.8 mg. per cent to a maximum of 6.5 mg. per cent at 8 hours. This is insignificant hemolysis. Occasionally, plasma hemoglobin levels remained at 2 mg. per cent (normal) throughout the dialysis.

Pressure recordings with a Hathaway strain gage oscilloscope and oscillograph showed maximum readings (in mm. of Hg) of 250/130 within the pumping chamber, 200 at the exit valve and 150/80 in the distal blood line. Morphologic studies of patients' blood after pumping for 8 hours showed no significant fall in white blood cell, red blood cell or platelet counts.

Postmyocardial Infarction Syndrome

William Dressler, New York, N. Y.

A complication of recent myocardial infarction has been observed in 25 patients, 18 of whom were admitted to the Maimonides Hospital during the last 2 years. The complication consists of 1 or a combination of these conditions: pericarditis, pleurisy or pneumonitis.

The clinical features are prolonged or recurrent fever and pain of the pleuropericardial type. A pericardial friction rub occurs more frequently and is of longer duration than in ordinary cases of myocardial infarction. It may occur for the first time several weeks after the onset of the illness, and it may repeatedly recur. There is frequently roentgenologic evidence of pericardial and pleural effusion. In some instances, pleural effusion or pneumonia dominates the clinical picture. Antibiotics do not affect the syndrome. Cortisone promptly abolishes pain and fever, and shortens the course of the attack.

The complication tends to relapse, thus prolonging the febrile course by many weeks or months. The outcome, however, has been favorable so far. The condition resembles closely the postcommissurotomy syndrome.

The postmyocardial infarction syndrome usually is not recognized, since it lends itself readily to mistaken interpretation. The most frequent erroneous diagnoses are: pulmonary embolism, extension of myocardial infarction, virus pneumonia and hemopericardium.

Factors Affecting Airway Resistance in Man

Arthur B. DuBois,† William A. Briscoe, Robert L. Burdick, and Jack Zabara, Philadelphia, Pa.

A specific method for measurement of airway resistance uncomplicated by the effects of tissue viscosity (DuBois, Botelho and Comroe, J. Clin. Invest. **35:** 327, 1956) has allowed appraisal of some factors determining airway resistance. Body size affects airway resistance, large adults having less and small adults more resistance (range 0.6 to 1.5 cm. H_2O/L./sec. at 0.5 L./sec.), probably because the dimensions of the airways depend on the size of the subject. Allowing for body size, subjects aged 4 to 87 years had similar resistances. Airway resistance was approximately inversely related to lung volume, being greater at residual volume and less at full inspiration. Change of dimensions of the airways probably corresponded with change of dimensions of the lungs. Pharmacologic actions: Oxygen in 1 breath produced no change of resistance, nor did oxygen breathed up to 6 hours (9 subjects). Although oxygen may produce atelectasis or ultimately lung damage, it is apparently not a bronchoconstrictor within 6 hours in normal man. After breathing 4 to 10 per cent CO_2 for 1 to 5 min., some subjects showed slight increase and others a slight decrease of airway resistance; the mean of 5 subjects did not change significantly. Denicotinized cigarettes inhaled produced no significant change; ordinary cigarettes, however, slightly increased the airway resistance. Aerosol of 3 per cent histamine moderately increased airway resistance. Cardiopulmonary diseases changed resistance; these changes are presumed to be due to the following mechanisms: (1) those affecting primarily the bronchial tree (e.g., bronchitis), (2) those originating in the lung tissue and encroaching on the airways (e.g., sarcoid), (3) fluid transudation from the pulmonary vascular bed into the tissues and airways (e.g., left ventricular failure) and (4) fibrotic retraction of the lung parenchyma yielded abnormally low airway resistance in 1 subject with scleroderma.

Criteria for Selection of Patients With Ventricular Septal Defects for Surgical Repair

James W. DuShane, Robert O. Brandenburg, Earl H. Wood, and John W. Kirklin, Rochester, Minn.

Surgical repair of ventricular septal defects employing extracorporeal circulation has been performed on 40 patients. Each patient was studied as completely as possible by cardiac catheterization, including selective dye-dilution curves and the effect of breathing oxygen, as well as by clinical evaluation. To avoid the effects of respiratory depression with anesthesia, studies of arterial oxygen saturation during exercise and while breathing air and oxygen were done on most of the patients who required anesthesia for catheterization. Experience with this group of patients has served to emphasize the importance of a critical individual evaluation of each patient with respect to the status of the pulmonary vasculature and intracardiac hemodynamics in relation to probable survival during the postoperative period.

Operation is recommended at present for those patients having increased pulmonary flow in spite of the degree of pulmonary hypertension or the presence of a right-to-left shunt. If the pulmonary flow is less than the systemic, surgical intervention is not recommended. Thus, selection of candidates for operation depends on proper assessment of the dominant intracardiac shunt. Criteria of importance are cardiac hyperactivity, roentgenographic signs of increased pulmonary blood flow, electrocardiographic evidence of increased left ventricular work, and the determination of intracardiac hemodynamics by cardiac catheterization, studies of arterial oxygen saturation and dye-dilution curves.

In many instances, the criteria of increased pulmonary flow are not clearly evident and selection for operation is extremely difficult. Systemic arterial oxygen desaturation suggesting right-to-left shunts may be secondary to anesthesia. Critical analysis of dye-dilution curves during catheteriza-

tion, studies of arterial saturation without anesthesia, and proper interpretation of the electrocardiogram with regard to atrial and ventricular dilatation are considered to be the most reliable means for determining dominant shunts and operability.

Effect of Exercise on the Growth of Coronary Arterial Anastomoses Subsequent to Coronary Arterial Narrowing in Dogs

Richard W. Eckstein,† Cleveland, Ohio.

Both coronary narrowing and occlusion, as well as myocardial hypoxia, anemia, and several surgical procedures, result in the growth of interarterial coronary anastomoses. Data as to the possible role of exercise as a stimulus to the development of collateral vessels are not available either in normal hearts, in hearts with coronary arterial narrowing, or in those with complete arterial occlusion. This report is concerned with 1 aspect of this problem, namely, the possible effect of exercise on collateral growth in the presence of various degrees of coronary arterial narrowing. Only dogs without functionally important collaterals were studied (i.e., those showing severe electrocardiogram changes following circumflex occlusion). The circumflex arteries were narrowed near their origins with braided silk. One half of the animals were rested in cages while the experimental group were exercised 20 min., 4 times daily, 5 days weekly for 6–8 weeks on a treadmill running at 4.7 m.p.h. up an incline of 30°. The extent of collateral development in each group was then assessed from measurements of the volume of retrograde circumflex flow made while mean aortic pressure was held at 100 mm. Hg. The degree of arterial narrowing was estimated from measurements of the rate of blood flow through the constricted arterial segment. Both values were expressed as flow per minute per 100 Gm. of myocardium. The data indicate that exercise is a significant additional stimulus to collateral growth above that provided by moderate circumflex narrowing in itself. The results to date also suggest that exercise in some instances effectively stimulates collateral growth to vessels which are only slightly narrowed.

Relationship of Serum Sodium Concentration, Serum Osmolarity, and Body Composition

Isidore S. Edelman,† M. Patrick O'Meara, and Lee W. Birkenfeld, San Francisco, Calif.

The concept of osmotic equilibrium across cell membranes has recently been challenged by studies on the in vitro behavior of tissues. The response to experimentally induced alterations in extracellular osmolarity, however, has been shown to conform to the concept of equality of osmotic pressures between the intracellular and extracellular phases.

To explore the question of osmotic equilibrium throughout body water, observations were made on the relationship between serum osmolarity and the quantities of exchangeable body sodium (Na_e), exchangeable body potassium (K_e), the principal osmotically active cations in the body, and total body water (TBW). Comparisons with simultaneous serum sodium concentration were also made since primary changes in intracellular osmolarity may be reflected in abnormalities of serum sodium concentration.

These 3 parameters of body composition were measured by isotope dilution methods using Na^{24}, K^{42} and D_2O as tracers, in 40 human subjects suffering from a variety of diseases. Twenty-eight subjects were edematous because of cardiac, hepatic or renal disease.

Serum osmolarity showed no correlation with Na_e, K_e, TBW or the ratios of Na_e/TBW or K_e/TBW. There was, however, a highly significant correlation between the sum of Na_e and K_e expressed per liter of body water $\frac{(Na_e + K_e)}{TBW}$ and serum osmolarity, with a slope of 1.98. Serum sodium concentration correlated closely with serum osmolarity when corrected for glucose and NPN. There was, in addition, a clearly significant correlation between serum sodium concentration and the ratio $\frac{Na_e + K_e}{TBW}$.

These results support the following conclusions: 1. Extracellular and intracellular fluids are in osmotic equilibrium, as a whole in vivo. 2. Serum sodium concentration is determined by the ratio of body sodium plus body potassium to body water.

Evaluation of Intermittent Claudication by Direct Stimulation Ergometry. II. Results after Arterial Reconstruction or Sympathectomy

Edward A. Edwards and Nancy L. Zimmerman, Boston, Mass.

Thirty-nine patients with peripheral arterial occlusion, mostly arteriosclerotic, were studied during a period of 6 months to 2 years. The calf muscles were stimulated by a rhythmic oscillating electric current, the foot acting against a variable load and the resultant movement recorded. The response of the ischemic muscles resembles that of fatigued normal muscles. The contractions are sluggish and of low amplitude; the relaxation is sluggish and incomplete, leading to a high residual tone (spasm). By continuing the stimulation for 3 min., an ergometric curve is produced whose total area may be taken as a quantitative statement of muscle power.

Thirteen patients were examined before and after reconstruction at aortic, iliac, or femoral levels. All showed substantial improvement in the individual contraction curves and in muscle power, but 2 to

3 months were required for this change, and it did not attain usual normal levels. Some patients demonstrated a later regression concomitant with secondary occlusion of graft or host arteries.

Twenty-six patients for whom lumbar sympathectomy had been performed were similarly studied. Improvement after operation was noted in about ⅓; it was equivocal in about ⅓, and lacking in the remainder. Improvement required 2 to 12 months for its manifestation; and it was more modest than after reconstruction (except in 1 patient with Buerger's disease). Some patients with great clinical improvement showed no change by ergometry. Deterioration after initial improvement could be correlated with progression of arteriosclerosis.

Drug Therapy of Essential Hypertension

Joseph C. Edwards, St. Louis, Mo.

Seventy-one hypertensives, 4 in the malignant phase, were treated during the past 3 years with the aid of rauwolfia, veratrum, hydralazine, hexamethonium, pentolinium and mecamylamine orally. Twelve of 23 on rauwolfia failed to get good results and other drugs had to be added. Of 28 on hexamethonium and hydralazine, 20 had successful control; 10 of these had average pretreatment diastolic blood pressures of 100 to 120 mm. Hg and 10 had above 120 mm. Hg diastolic pressure. Nineteen of 23 on pentolinium and reserpine and/or hydralazine had good control. Twelve patients with moderately severe to severe hypertension were treated with mecamylamine after failure to respond to reserpine alone. Three failed to respond with even control of blood pressure until hydralazine was added.

Success was measured by the reduction of supine diastolic blood pressure to 100 mm. Hg or lower, and systolic blood pressure to 160 mm. Hg or less most of the time.

Eleven of the 23 patients treated with pentolinium and the other drugs had diastolic blood pressures of 100 to 120 mm. Hg before therapy. Ten of these had satisfactory control.

Three patients developed severe depression with paranoid and suicidal trends while taking reserpine and therefore it was discontinued.

Five patients developed a rheumatoid or lupus-like febrile reaction with tender swollen joints that disappeared when hydralazine was discontinued.

Three patients who were treated with ganglionic blocking agents and apresoline for over 2 years have been normotensive without any medication except 1, who is still on reserpine.

The necessity of careful instructions to the patient in the pharmacology of these drugs, helping the patient achieve better emotional adjustment, and complete cooperation of the intelligent patient when treated in the office or home is essential and cannot be overemphasized. A system of grading the patients according to severity will be presented as an aid to the proper selection of therapy.

Intracardiac Angiography: Instantaneous Release of Contrast Material Within the Heart

John C. Elder, Bernard L. Charms, and Bernard L. Brofman, Cleveland, Ohio

By means of a special catheter with an inflatable balloon tip, large volumes of contrast material can be liberated within the right heart chambers. A simple wire-release mechanism provides controlled instantaneous evacuation of the balloon. In more than 25 patients, subjective reactions have been milder than with standard injection technics.

Left heart and aortic visualization is improved by the high concentration of dye. The method has proved particularly helpful in patients with rheumatic heart disease. Timing of the concentrated bolus as it reaches the left atrium and the duration of opacification of the left atrium and left ventricle gives an indication of hemodynamics at the mitral valve. In a series of patients with atypical physical findings, intracardiac angiography demonstrated evidence of mitral stenosis which diagnosis was confirmed at operation.

In patients with congenital heart disease, excellent selective visualization of defects can be achieved. Since the material contained in the balloon is incompressible, sudden liberation does not significantly alter hemodynamics. Liberation of the dye beyond a left-to-right shunt provides for visualization of the shunt when the dye reaches the left heart, without residual opacification of the right heart. The internal architecture of the right heart chambers is well-demonstrated, particularly in valvular and infundibular pulmonic stenosis. In a patient with congenital absence of the left pulmonary artery, excellent visualization was provided by liberation of the dye in the right atrium.

General anesthesia is unnecessary, so that maximum patient cooperation is obtained. Positioning the patient is particularly easy since the arm used need not be elevated for the injection. Repeat studies have been carried out without ill effects.

A Follow-up Study of 1000 Patients with Mitral Stenosis Undergoing Valvuloplasty

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Nineteen group II, 709 group III and 272 group IV patients with a preoperative diagnosis of predominant mitral stenosis were operated on between November 1949 and March 1956. The operative mortality in the second 500 patients was 0.6 per cent in groups II and III, and 20 per cent in group IV. Of the 913 patients who survived operation, 825 have been followed from 1 to 5 years including 27 who died within the first year.

Seventy-seven per cent of groups II and III patients and 62 per cent of group IV patients, were moderately to markedly improved at the latest follow-up. These percentages were similar in the groups of patients followed for the longer periods as compared to those followed for only 1 to 2 years. The survival rate in groups II and III has been 89 per cent at 4 years and 88 per cent at 5 years compared to survival rates of 68 per cent and 60 per cent in a comparable series of medically treated patients reported by Olesen. In group IV, the survival rates at 4 and 5 years were 72 per cent for the operated patients and 14 and 11 per cent for those medically treated.

The effects of age, atrial fibrillation, associated mitral insufficiency and aortic valve disease on clinical results will be discussed. Evidence will be presented that significant refusion of the valves has occurred rarely within the period of observation, and that a poor result is more often due to an inadequate valvuloplasty or to other factors.

One hundred and eighty-six patients of the 1000 had had 1 or more clear-cut episodes of preoperative embolization. The incidence of operative embolization in the last 500 operated cases was 2 per cent in groups II and III and 9 per cent in group IV. Nineteen patients of the entire group who survived operation had had late peripheral emboli, suggesting that the operation protects against late embolization.

Blood Pressure Studies in Two Infants with Coarctation of the Aorta and Patent Ductus Arteriosus

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It is quite difficult to study the blood pressure variations in infants using the conventional auscultatory and palpatory technics. With the aid of the "flush" blood pressure technic, described by 1 of us previously, and simultaneous use of a sensitive electric microphone, it was possible to follow the blood pressure changes in 2 infants with a combination of coarctation of the aorta and patent ductus arteriosus before, during, and after surgery.

A modification of the flush technic, in which the systolic pressures in an arm and a leg were determined simultaneously, was combined with a sensitive electric microphone which replaces the stethoscope and is attached to a toe or thumb. The latter method records directly on an electrocardiographic machine and has been checked previously with simultaneous direct intra-arterial electromanometric determinations in monkeys with excellent correlation.

The diagnosis of coarctation was confirmed on admittance to the hospital in both babies with the aid of the flush method. The first baby's systolic pressure by the flush method was 71 mm. Hg in both arms and 41 mm. Hg in both legs. Simultaneous determinations made with the electric microphone were 85 mm. Hg in the arms and 35 mm. Hg in the legs, a pressure difference by both methods of 30 mm. Hg between the upper and lower extremities. Following surgery, the systolic pressure in the legs came up and the pressure difference between the arms and legs was reduced to 0 to 10 mm. Hg.

The second baby's systolic pressure by the flush method in the arms was 147 mm. Hg and in the legs 47 mm. Hg, a difference of 100 mm. Hg, while pressures obtained with the electric microphone were 162 mm. Hg in the arms and 55 mm. Hg in the legs, a pressure difference of 107 mm. Hg. In this case, the systolic pressure by the flush method in the arms after surgery was 136 mm. Hg and in the legs 104 mm. Hg, with a difference of 32 mm. Hg, and by the electric microphone it was 155 mm. Hg in the arms and 120 mm. Hg in the legs, with a difference of 35 mm. Hg between them.

In conclusion, the value of the flush method, especially for revealing differences in blood pressure between the upper and lower extremities, was demonstrated, and the electric microphone was found to be an excellent and simple tool for following graphically the blood pressure of infants undergoing major surgery.

Factors Associated with Geographic Differences in Deaths from Coronary Heart Disease

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Within the continental United States the reported mortality from coronary heart disease (list no. 420) differs greatly. In 1950 the death rate among white males in the age group 65–74, for example, ranged from 11.6/1,000 population in the East South Central states (Ky., Tenn., Ala., Miss.) to 19.6 in the Middle Atlantic states (N. Y., N. J., Pa.). These differences appear to be real. They cannot be explained in terms of other cause of death classifications which might be confused with coronary heart disease. Moreover, they are reflected in differences in the death rates from all causes (44.6/1,000 in E.S.C. states vs. 54.0 in M.A. states). They do not appear to be due to migration of populations about to die or to differences in urbanization (differences persist if only rural areas are compared).

Differences in the death rates from coronary heart disease might be associated with ethnic differences of populations in various parts of the country. Heights of draftees in World War I from each of the states were compared with the death rates experienced in those states in the age group 45–64 during the year 1949–51. It was found that states having the shorter draftees in World War I had the higher death rates from coronary heart disease in 1949–51. The 1950 census reveals that immigrants from southern and eastern Europe (ethnic groups characterized by short stocky body builds in World

War I) have settled largely in those areas which are now experiencing high death rates from coronary heart disease.

These observations support others to the effect that genetic (or associated cultural) factors may be importantly related to coronary heart disease.

Vasodepressor Syncope: Effect of G-Suit Inflation on the Cardiac Output

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Vasodepressor syncope is characterized hemodynamically by a diminished peripheral resistance and fall in blood pressure. Cardiac output studies have demonstrated the failure of the heart to compensate for the suddenly diminished peripheral resistance. This failure may result from either reflex cardiac inhibition or diminished venous return secondary to peripheral pooling. In attempting to evaluate the role of the latter factor the effects of G-suit inflation on the hemodynamic changes in vasodepressor syncope have been studied.

Cardiac output by the dye dilution technic was determined in 12 normal volunteers at 60° head-up tilt before and immediately after G-suit inflation, and in 8 of the above subjects following G-suit inflation in postural syncope. In all of the above a single balloon-type half-body anti-gravity suit was inflated within 10 sec. to 60 mm. Hg, body pressure and cardiac output determinations were performed during the initial 30 sec. following full inflation.

G-suit inflation in normal erect subjects results in increased cardiac index (mean change 2.4 to 3.0 L.), mildly increased systolic and diastolic arterial pressures (8–12 mm.), and a fall in calculated peripheral resistance (mean change 1430 to 1180 units). G-suit inflation reverses the clinical changes in syncope within 30 sec. In these subjects the rise in cardiac output and arterial pressure is larger, yet peripheral resistance does not significantly change from the low syncopal value.

The effectiveness of G-suit inflation in reversing the hemodynamic changes of vasodepressor syncope is probably related to its ability to promptly elevate venous return to the heart. The cardiac output changes concomitant with the recovery after inflation is presumably secondary to this effect. Although these studies have not eliminated the factor of reflex cardiac inhibition they point to the significant role of the venous return in modifying the cardiac response to the diminished peripheral resistance in vasodepressor syncope.

Streptococcal Cardiac Lesions in Rabbits

Peter E. Fehr, Joel G. Brunson, and Richard L. Davis, Minneapolis, Minn.

Paired hybrid albino rabbits were subjected to carotid artery-jugular vein cross circulation for a period of time not exceeding 45 min. This was accomplished by the use of polyethylene catheters inserted into the vessels, and small amounts of heparin sodium as the anticoagulant. During cross circulation, or at varying intervals before or after the procedure, each rabbit was given a single intravenous injection of 3 ml. of a 24-hour broth culture of *Streptococcus viridans*. The animals died or were killed 6 days to 2 weeks following administration of the bacteria. Similar arteriovenous shunt experiments were performed in individual rabbits by connecting the carotid artery to the jugular vein for periods not exceeding 45 min.

Thirty per cent of the 72 animals subjected to these procedures developed gross valvular lesions. These consisted of large, firm, opaque nodules along the free margins of the mitral or aortic valves, or both. These were the only valvular lesions in which bacteria were demonstrated. However, 63 per cent of the animals showed microscopic lesions of the valves and coronary arteries. These lesions were characterized by the presence of extensive accumulations of fibrinoid within the substance of the valves and within the walls and lumens of the arteries, associated with a cellular reaction composed of Anitschkow cells, large mononuclears, and fibroblasts. The arterial lesions were occasionally associated with large areas of ischemic necrosis of the muscle. None of 16 animals subjected to cross circulation alone developed bacterial lesions, and only 2 of 26 animals given streptococci alone showed gross valvular lesions.

These observations suggest that such technics may permit localization of specific micro-organisms in the heart, and may allow closer investigation of the role of group A hemolytic streptococci in the pathogenesis of rheumatic carditis.

Prednisone in Acute Rheumatic Carditis: Observations on Seventeen Patients

Charlotte Ferencz, Milton Markowitz, and Joseph J. Bunim, Bethesda, Md.

Recent experience in the therapy of early rheumatic carditis suggests the use of high doses of steroid over a long period of time.

Seventeen children received prednisone for a period of 14 weeks with an aggregate dose averaging 4.5 Gm. Observations on the clinical, metabolic and toxic effects of this drug are reported.

Fourteen patients were in their first attack of rheumatic fever. All had unequivocal evidence of carditis. All were treated within 1 month from onset of their disease. The children were on bedrest and received a normal ward diet.

The anti-inflammatory effect of prednisone paralleled that of cortisone.

Six to 12 months after cessation of therapy, 11 of the 17 patients had no evidence of residual cardiac

damage, 2 had questionable heart disease, and 4 had rheumatic heart disease. Of these 4 all had moderately severe carditis at onset, and 3 had been treated within the first week of their illness.

Side effects of therapy were noted in all patients and included marked facial rounding, abdominal distention, hirsutism, striae and acne. Three children developed hypertension; in 1 a convulsive seizure occurred.

Biochemical studies in 12 patients revealed no gross abnormality of serum electrolytes. In 4 children a slight rise in serum CO_2 occurred, but was not accompanied by hypopotassemia. Growth was temporarily arrested and excessive weight gain occurred during therapy. None of the patients developed edema or congestive heart failure.

When the drug was reduced or discontinued manifestations of activity reappeared temporarily in 15 patients. Tachycardia, fever, elevated ESR and positive CRP occurred in 7 during the period of reduced dosage. Following therapy heart murmurs reappeared in 8 children and disappeared spontaneously.

Hypertension and Pyelonephritis Masquerading as Toxemia of Pregnancy: An Analysis of 1,081 Cases Followed by an Internist

Frank A. Finnerty, Jr., Washington, D. C.*

Serial studies on 1,081 "toxemia-suspect" patients have revealed that hypertensive vascular disease and pyelonephritis frequently masquerade as toxemia of pregnancy. The triad (or any part) of an elevated blood pressure, edema and albuminuria has been seen in each of these diseases. Experience has suggested that ophthalmoscopic examination and a complete urinalysis permit prompt differentiation of these diseases.

Toxemia is said to exist when the ophthalmoscopic examination reveals a retinal sheen and normal arteries, and urinalysis reveals only albuminuria. Hypertensive vascular disease exists when the retinal arteries show hypertensive changes and no retinal sheen is present. When both hypertensive changes and a retinal sheen are seen on ophthalmoscopic examination, with or without albuminuria, toxemia is then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggests pyelonephritis; clumps of white cells and glitter cells document the diagnosis. Though a retinal sheen and albuminuria are seen in both toxemia and acute glomerulonephritis, microscopic hematuria (occasionally gross hematuria) is seen more commonly in glomerulonephritis.

Though 95 per cent of the patients referred to the clinic originally had the diagnosis of toxemia, only 13 per cent had toxemia by our criteria. Our diagnoses included hypertensive vascular disease (666), hypertensive vascular disease plus superimposed toxemia (90), postpartum hypertension (72), pure toxemia (154), pyelonephritis (56), edema without disease (38), and unrelated cardiac or renal disease (5).

The ability to differentiate these disease states provided the opportunity to study whether toxemia caused vascular damage. One hundred twenty-five of the pure toxemia group 6 weeks postpartum revealed no abnormality. In 29 patients, however, despite return of the blood pressure to normal and disappearance of edema and albuminuria, examination of the retina revealed definite retinopathy. These retinal changes are attributed to the duration of the toxemia rather than to its severity.

Incrimination of the Capillary Bed in the Pathogenesis of Acute Hypertension

Frank A Finnerty, Jr., Robert L. Guillaudeu, and Joachim H. Buchholz, Washington, D. C.*

Many investigators have demonstrated that severe toxemia of pregnancy is associated with hemoconcentration and that clinical improvement is associated with gradual blood dilution. Observations in 4 patients with severe toxemia of pregnancy (2 patients with eclampsia) have shown a 25 per cent increase in plasma volume and decrease in hematocrit immediately following reduction of arterial pressure. To determine the specificity of these changes for toxemia and perhaps to throw light on the pathogenesis of a fluid shift, serial plasma volume determinations (T1824) were performed before and immediately after acute reduction of arterial pressure in 3 groups of patients. Serial cardiac output determinations were also performed in order that the mean circulation time and central blood volume might be calculated.

Acute reduction of arterial pressure in 4 patients with moderately severe toxemia was accompanied by an 18 $\pm$ 28 per cent increase in plasma volume. Acute reduction in arterial pressure in 7 nonpregnant patients with chronic hypertension and 2 normotensive patients was accompanied by no change in either plasma volume or hematocrit. In 6 patients with acute hypertension (2 malignant, 1 encephalopathy, 2 with recent, flame-shaped hemorrhages in the fundi, 1 postpartum hypertension), a 33 per cent reduction of arterial pressure was accompanied by a 26 $\pm$ 11.3 per cent increase in plasma volume and decrease in hematocrit.

These changes seemed to be unrelated to either the drug given, or secondary to a change in cardiac output, since veratrum was used in 2 instances, hexamethonium in 2 and hydralazine in 3 instances and the cardiac output was elevated in 3 and decreased in 3 instances.

It would seem from these data that: (1) hemoconcentration is not a specific finding for toxemia of pregnancy but is present in any *acute* hypertensive state, regardless of cause, and (2) acute reduction of arterial pressure under such circumstances is accompanied by hemodilution. Although the cause

of this hemodilution remains unknown, it would seem that the capillary bed must be incriminated in some fashion to explain this shift in fluid. Studies to determine whether such acute reduction in arterial pressure is related to an increase in the oncotic pressure or a decrease in the capillary filtration pressure are in progress.

Right and Left Atrium Needle Puncture for Simultaneous Right and Left Heart Catheterization

Don L. Fisher and Maurice M. McCaffrey, Pittsburgh, Pa.

A procedure of right heart catheterization via percutaneous right atrium needle puncture has been developed for use with the similar method of transthoracic left heart catheterization in rheumatic valve disease. The addition of right heart catheterization to the test is desirable in order that the pressure effects of right-sided valve lesions or ventricular failure may be detected, and so that a pulmonary artery blood sample may be obtained for the Fick cardiac output determination.

Intermittent fluoroscopic observation is used for monitoring needle positions during the advance toward the right and left atria, respectively, insuring that the needle tips do not arrive at other locations. The right paravertebral approach is used in each instance, with the patient in the prone position. Appropriate sites for needle insertion are selected according to the appearance of the cardiac silhouette, and standard geometric factors assist in placement of the left atrial needle, as previously reported.

The right atrial needle is inserted 1 interspace lower than the left atrial needle, at a distance 3½–4 cm. to the right of the palpable spines, with an angle of 12–18° toward the left from the perpendicular. The needle is placed with a slightly caudad direction, toward the right atrial segment of the cardiac shadow. A flexible polyethylene catheter is then inserted through the needle, and is advanced to the pulmonary artery. Additional procedures of exercise in the prone position, and injection of tracer substances are performed in selected cases.

Such combined heart catheterization tests have been performed in a series of over 40 patients, with no serious complications. Right pneumothorax occurred in 1 instance, and was relieved by aspiration. Right heart catheterization via percutaneous right atrium puncture is indicated as a simultaneous procedure with transthoracic left heart catheterization, because of its convenience in this use.

Circulation and Respiration in Kyphoscoliosis

Alfred P. Fishman,† Edward H. Bergofsky, Gerard M. Turino, A. Gregory Jameson, and Dickinson W. Richards, New York, N. Y.

The present study was designed to explore 3 broad groups of pathophysiologic mechanisms which may contribute to alterations in respiration and circulation in kyphoscoliosis: (1) inhomogeneity in distribution of inspired gas and mixed blood within the lung; (2) impaired diffusion of O_2 and CO_2 across the alveolar-capillary interface; and (3) increased work of the right heart associated with pulmonary hypertension and terminating in cor pulmonale.

Observations were carried out on 15 kyphoscoliotic subjects. The methods used included: (a) measurement of lung volumes by standard technics; (b) analysis of arterial blood and expired gas for evaluation of gas exchange; (c) right heart catheterization for the determination of pulmonary artery and pulmonary wedge pressure and cardiac output; and (d) bronchography and angiocardiography for the estimation of the degree of distortion of intrathoracic structures.

The results indicate that generalized alveolar hypoventilation is a prime defect in these subjects, leading to arterial hypoxemia and hypercapnia. In contrast to chronic pulmonary emphysema, the alveolar hypoventilation is due to anatomic restriction of the chest bellows rather than to bronchial obstruction and uneven distribution of inspired gas. Pulmonary hypertension exists in some subjects at rest and is elicited in others during exercise by small increments in blood flow. Since pulmonary hypertension may occur during exercise in the absence of either arterial hypoxemia or back pressure from pulmonary veins, the principal mechanism underlying the pressor response appears to be a relatively augmented blood flow into an anatomically restricted vascular bed.

The therapeutic implications of these studies relate to the improvement in alveolar hypoventilation. Mechanical respirators are of value despite deformed and apparently rigid chests. The results also emphasize the hazards entailed in the use of sedatives or oxygen therapy in the presence of alveolar hypoventilation, CO_2 retention and secondary depression of the respiratory center.

Tissue Culture Studies in Rheumatic Fever

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A delayed hypersensitivity of the tuberculin type is one of the more common theories of causation of rheumatic fever. Since measurement of this type of sensitivity has been reported in tissue culture rheumatic and nonrheumatic tissues have been compared in their responses to crude streptococcal filtrates and to disintegrated organisms derived from strains presumed to have caused the disease, both in the presence of pooled serum from normal individuals as well as in serum from rheumatic fever cases. Migration was observed after 1 day, and spindle-shaped transformation of certain white blood cells was measured about 1 week after explantation in both rheumatic and nonrheumatic bloods. The effect on migration after phagocytosis of dead

streptococci by rheumatic and nonrheumatic white blood cells was likewise observed. Fibroblasts were compared from skin and heart auricular tips of rheumatic and nonrheumatic individuals and from an occasional rheumatic nodule grown in various concentrations of those same materials. Using similar tissue culture technics, we also re-examined the concepts involved in the delayed type of tuberculin hypersensitivity using tissues from tuberculous and nontuberculous humans and guinea pigs. Our results in these experiments were not nearly as definitive as many of the reports in the literature. Although statistical evaluation of grouped data suggests some differences in the responses between certain normal and rheumatic fever tissues, we were not able to demonstrate, by the use of our tissue culture technics, an "all or none phenomenon" that would clearly distinguish a rheumatic from a nonrheumatic individual. A statistically measurable hypersensitivity probably does exist, an individually demonstrable one does not.

Treatment of Gangrene of the Feet and Legs by Walking

William T. Foley, New York, N. Y.

Necrosis of the lower extremities has invariably led to the complete bed rest of the patient. The present editions of commonly used medical texts in discussing the treatment of such patients assume that they are confined to bed.

Bed rest results in decreased blood flow. Disuse atrophy follows. Bone is absorbed. Muscles waste. The skin looses its turgor. Nails and hair grow less rapidly. Pulses become less strong. Dietrick showed that at bed rest patients were in negative nitrogen and calcium balance. They also demonstrated that this process could be reversed by keeping the patient in motion in an oscillating bed.

The greatest stimulus to collateral blood flow in the legs is walking. Thoma in 1884 found that the growth of collateral blood vessels was directly proportional to blood flow through them. This work was confirmed by Lewis.

A group of 23 patients with demarcated gangrene, most of whom were bed-ridden for many months, were carefully selected for a trial of weight bearing. This was in addition to a conservative regimen of: (1) abstinence from tobacco; (2) the aid of gravity (oscillating bed); (3) warmth; (4) local antimicrobial ointments and gentle débridement; (5) release of vasospasm; (6) induced fever in certain cases; (7) anticoagulants in complicating phlebitis or cases of embolization; (8) the usual treatment of associated diabetes mellitus and cardiac insufficiency.

Where multiple therapeutic measures are employed, credit cannot rightly be given to 1 alone. The introduction of walking appears to have aided healing. Twenty-two of the 23 cases healed completely with only minor loss of tissue. The failure occurred in a patient who refused to walk at home because her family objected.

The profession should reconsider the time-honored custom of insisting on bed rest for patients with gangrene of feet or legs from arterial insufficiency. Walking decreases the need for nursing attendance. It allows some patients to be treated at home. Some are able to return to work, even with gangrenous toes, and be treated ambulatory.

Case histories will be illustrated with colored projection slides, showing the necrotic lesions and the various stages of healing.

Rationale of Venous Occlusion Plethysmography

Paul F. Formel and Joseph T. Doyle, Albany, N. Y.

The validity of the venous occlusion method of plethysmography rests upon the assumptions that for an indeterminate period the arterial inflow into the occluded segment is unaltered, the venous outflow is completely interrupted and the impounded blood causes the occluded segment to swell proportionally. These assumptions have been generally accepted without having been systematically investigated. The following studies were therefore undertaken.

A modified water displacement plethysmograph, with a strain gage sensing unit, was used. The venous pressure within the occluded forearm segment, the brachial arterial pressure, and the occluding cuff pressure were recorded simultaneously with the plethysmogram.

Visual integration of the slope of the plethysmogram demonstrates that the rate of arterial inflow is essentially unaltered until the venous pressure in the occluded segment reaches a level of 20–30 cm. of water. Thereafter, inflow appears to fall off in proportion to the diminution in the arteriovenous pressure gradient. These data suggest that the arterial inflow into the occluded segment is initially not significantly changed, and that the venous outflow is completely or partially impounded at a constant rate.

When radioiodinated serum albumin is injected into a dorsal vein of the hand, specific activity in the arm just proximal to a venous occluding cuff rises abruptly at the moment when the venous pressure in the occluded segment equilibrates with the cuff pressure. It is deduced that until this moment the occluding cuff completely obstructs the venous return.

If the hindleg of an experimental animal be excluded by a crushing tourniquet from the systemic circulation except for the femoral artery and vein, the increase in the volume of the leg following obstruction of the femoral vein is proportional to the metered arterial inflow.

It is felt that these observations satisfactorily

validate the venous occlusion method of plethysmography.

Hemodynamic Effects of Hypervolemia With and Without Anemia

Noble O. Fowler, Walter L. Bloom, John A. Ward, and Robert H. Franch, Atlanta, Ga.

This study was made to elucidate the mechanism of increased cardiac output occurring after large infusions of Dextran. Eleven dogs received 2 infusions each of 6 per cent Dextran equal to 2 per cent, 3 per cent, and 3 per cent of body weight respectively. Seven others received the same volume of matched heparinized blood. Hemodynamic measurements were made in a control period and 20–30 min. after each infusion. Total blood volume increased 90 per cent in the Dextran-infused dogs and 85 per cent in blood-infused dogs. Mean hematocrit fell significantly from 36 to 13 in the Dextran-infused group and rose, but not significantly, from 41 to 47 in the blood-infused animal.

Fick cardiac outputs (in ml./Kg./min.) rose significantly from 163 ± 26 to 293 ± 58 in the Dextran-infused dogs and fell, but not significantly, from 179 ± 30 to 122 ± 11 in the blood-infused dogs. In the blood-infused dogs, there was no significant change in systemic, pulmonary, or right atrial mean pressures. In the Dextran-infused dogs, right atrial mean pressures rose 5.6 ± 1.5 mm. Hg, $p < 0.01$, and pulmonary arterial pressures rose 11.2 ± 2.3 mm. Hg, $p < 0.001$.

Although blood and dextran infusions produced equal expansion of total blood volume, Dextran infusion increased cardiac output and right atrial and pulmonary arterial pressures, whereas blood infusion did not. The data to be presented suggest that 2 major factors may be responsible for the difference in hemodynamic effect of blood and dextran infusion: (1) the production by Dextran infusion of dilution anemia, which does not occur with blood infusion; and (2) an apparent greater increase in ease of expansibility of the vascular system following blood infusion, which allows an increase in total blood volume without accompanying rise in right atrial and pulmonary arterial pressures.

Hemodynamic Effects of Large Dose Infusions of l-Norepinephrine During Pulmonary Arterial Constriction

Noble O. Fowler, Robert H. Franch, and Edward R. Duchesne, Atlanta, Ga.

Unpublished observations have shown that l-norepinephrine infusion increases the cardiac output of the anesthetized dog. The present study was undertaken to ascertain whether norepinephrine can increase cardiac output in the intact animal with increased cardiac work load. The main pulmonary artery of 11 dogs was progressively constricted until 1 of the following occurred: right ventricular systolic pressure increased to 50–70 mm. Hg; dilatation of the right ventricle was observed; or until systemic arterial pressure fell (period 1). l-Norepinephrine, 3–6 μg./Kg./min. was then infused for 15–30 min. (period 2). After a 15 min. recovery (period 3), a second infusion of norepinephrine was given (period 4). During the control period and periods 1–4, measurements were made of pulmonary arterial, right atrial and carotid arterial pressures, and of direct Fick cardiac output.

Control cardiac outputs were 118 ± 15 ml./Kg./min. With pulmonary arterial constriction, cardiac outputs fell significantly, 69 ± 14 ml./Kg./min., $p < 0.05$. During the first l-norepinephrine infusion, cardiac outputs increased significantly, 124 ± 14 ml./Kg./min., $p < 0.01$. After discontinuance of l-norepinephrine, cardiac outputs fell significantly to 51 ± 7 ml./Kg./min., $p < 0.001$. During a second l-norepinephrine infusion, a significant increase in cardiac output to 118 ± 18 ml./Kg./min., $p < 0.01$ again occurred. During l-norepinephrine infusion, heart rate increased significantly, systemic arterial pressure rose significantly, and the dilated heart decreased in size. Elevated right atrial pressure associated with acute right ventricular failure due to pulmonary arterial constriction was lowered by infusion of l-norepinephrine. It is concluded that infusion of l-norepinephrine in the presence of acute induced pulmonary arterial constriction produces the following effects: increase in cardiac output, increase in heart rate, reduction in size of the acutely dilated right heart.

A New Dye for Continuous Recording of Dilution Curves in Whole Blood Independent of Variations in Blood Oxygen Saturation

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A serious disadvantage of the valuable application of oximeters and densitometers to the continuous recording of indicator-dilution curves in whole blood is the fact that these instruments cannot distinguish between variations in the concentration of oxyhemoglobin and reduced hemoglobin and the indicators used (usually Evans blue). A suitable indicator with high spectral absorption at a wave length equally absorbed by oxyhemoglobin and reduced hemoglobin (such as 800 mμ) would circumvent this disadvantage and permit recording of dilution curves on the venous side of the circulation as well as in arterial blood in spite of variations in blood oxygen saturation.

A compound (dye I) belonging to the tricarbocyanine group of dyes and having the requisite absorption at 800 mμ has been developed. It is

stable for months in propylene glycol. In equal concentrations in plasma (2.4 mg./L.), dye I has an optical density at 800 mμ of 0.84, which is more than 4 times greater than the optical density of T-1824 at the wave length (640 mμ) used for its detection by oximetry.

Dye I is bound to plasma proteins (dye-free dialysate) and can be quantitatively determined in plasma or blood. Rapid injection of 0.1 mg./Kg. body weight produces circulatory dilution curves that can be recorded satisfactorily by oximetry.

This dose produced no detectable acute or chronic alteration in the dog. The approximate lethal intravenous single dose was 5 mg./Kg. for guinea pigs and cats and 15 mg./Kg. for dogs. This dye probably will prove of great value in diagnosis by arterial dilution technics in cyanotic heart disease and in investigations during hypoxia or by application of dilution technics in the venous circulation.

Fibrinogen Polymerization Test in Nonspecific Myocarditis and Pericarditis

Rudolph E. Fremont, Samuel Losner, and Bruno W. Volk, Brooklyn, N. Y.

A new laboratory procedure found to be highly specific in active rheumatic diseases was employed to investigate anew the relationship between nonspecific myocarditis and pericarditis, and acute rheumatic fever.

This so-called Fibrinogen Polymerization (F.P.) test utilizes blood treated with small amounts of heparin. Three hours following coagulation, the serum is tested for fibrinogen. This was found more rapidly consumed in active rheumatic diseases than in normals or nonrheumatic conditions.

F.P. tests were obtained serially and correlated with clinical and laboratory data including all "acute phase reactants" in the following conditions: A. Myocarditis, nonspecific (3); rheumatic (4); questionable (2). B. Pericarditis, nonspecific (5 with 6 episodes); associated with rheumatic valvular disease (2); tuberculous (1); probably tuberculous (2). C. Combined myo- and pericarditis, rheumatic (1); nonspecific (1).

The F.P. test was uniformly positive in nonspecific myocarditis and also in rheumatic myocarditis, and negative in questionable myocarditis. Correlation with the acute phase reactants was good only in rheumatic myocarditis. Correlation with the clinical and remaining laboratory findings was quite similar in nonspecific and rheumatic myocarditis. The F.P. test remained frequently positive after all other findings had returned to normal.

The F.P. test was uniformly positive in acute nonspecific pericarditis and also in the 2 rheumatic cardiacs with acute pericarditis 1 of which represented a postcommissurotomy syndrome. It was negative in the "tuberculous" group. Correlation with the acute phase reactants was good both in the nonspecific and rheumatic group. Correlation proved also good between serial F.P. tests and electrocardiographic changes, both in the nonspecific group and the 1 rheumatic case so studied.

These preliminary observations suggest strongly a common bond between nonspecific myo- and pericarditis and acute rheumatic fever, be it called "rheumatic" or "hyperergic." Further experimental and clinical work regarding this challenging matter is in progress.

Sodium and the Mechanism of Blood Pressure Elevation

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The distribution of water, sodium, and potassium was measured in the rat under various conditions which elevate or depress the blood pressure. Inulin, after a 2-hour period of equilibration in the recently nephrectomized rat, was used to indicate the extracellular fluid volume. Extracellular sodium and potassium were measured as the product of extracellular fluid volume and the concentration of these ions as determined by flame photometry in plasma. Blood pressure was followed electromanometrically. The pressor or depressor agent, in a saline medium, was injected intravenously in 1 group and controlled by saline alone in another. The variables under study were measured at intervals of 1 min. to 1 hour after injection, using at least 8 control and 8 test rats for each interval.

Pitressin was observed to have a primary extrarenal action with doses ranging as low as 1 milliunit. The elevation in blood pressure correlates directly with the entrance of sodium and water into cells. The same process occurred with both adrenaline and noradrenaline. While Pitressin and adrenaline-noradrenaline both affect the sodium transfer system, the mechanisms seem to be different since the Pitressin effects are not blocked by dibenzyline and, further, noradrenaline is still effective in the Pitressin-refractory animal. The effects of histamine are in the reverse direction to those of the above pressor agents.

It has previously been demonstrated that an alteration in sodium tolerance is a characteristic common to many forms of chronic experimental hypertension. Using DCA as a typical agent, it can be shown that before the blood pressure is actually elevated, there is already a heightened sensitivity to Pitressin and noradrenaline, agents which, according to the work reported here, affect the blood pressure through sodium transfer.

From these investigations we suggest as a theory that peripheral vascular resistance depends on the "sodium transfer systems" broadly defined, which govern the dynamic equilibrium between sodium entrance and extrusion in vascular smooth muscle.

Effects of Venous Tourniquets on the Distribution of Blood

Hugo Garcia, Richard L. Birchfield, William H. Knisely, and John M. Wallace, Durham, N. C.*

Blood pressure cuffs were placed high on the thighs of 7 fasting resting recumbent adult males. The legs were congested by pressures between 80 and 90 mm. Hg for 10 min. The circulation was then stopped by raising the cuffs above arterial pressures. Cr^{51} tagged erythrocytes were injected into an arm vein. During the 10 to 14 min. of arterial occlusion and for 90 min. thereafter samples were drawn from the opposite arm. Ninety-three to 96 per cent of the injected Cr was attached to erythrocytes. Counts/min./ml. packed erythrocytes were calculated using the mean of from 2 to 4 capillary hematocrits.

During occlusion the average erythrocyte volume was 1701 ml. and following cuff release 2340 ml., 27.3 per cent being pooled. The average hematocrit during occlusion was 45.1 and reached a maximum of 47.3 following release. Assuming 45.1 as the initial hematocrit for all pooled blood, and using the maximum venous hematocrit values and the percentages of trapped cells, the hematocrit of the blood leaving the congested area was calculated to be 53.2, 18 per cent above the entering blood. Assuming constant erythrocyte volume in the legs (average 639 ml.), the plasma entering them was calculated to be 778 ml. and leaving was 562 ml. with 216 ml. of fluid lost during occlusion. Following release of cuffs the Cr^{51} tagged cells were mixed in 1 min. in 3 subjects, and within 5 in 3 others. The maximum hematocrits coincided with the first mixed Cr^{51} samples. The venous hematocrits continued to fall for approximately 30 min.

Because the Cr^{51} was rapidly mixed while the hematocrit continued to fall, we concluded that the slow change in the latter is not a result of mixing but represents the return of fluid from the legs.

Electrocardiogram in Infancy

Manuel Gardberg and Irving L. Rosen, New Orleans, La.

In our laboratory we have been making electrocardiograms and vectorcardiograms on healthy infants beginning no later than age 1 month; then at intervals of 3 to 6 months. Many of the children whose electrocardiograms have been recorded serially in this fashion are now 2 years old.

This approach to the study of the electrocardiograms of the infant has yielded observations which are important. Some generalization regarding the evolution of the electrocardiogram during the first 2 years of life are possible. Marked right axis deviation as reported by others does not persist throughout infancy, although it is common in older children and adults. The evolutions of the high R in V_1 is extremely variable; it may persist into the second year, or may be replaced by an RS within 3 months. Evaluation of the high R in V_1 requires recognition of the frequent occurrence of right bundle-branch delay in young infants, a phenomena which apparently disappears in most cases a little later. The placement of the electrode in some infants, as in some adults, frequently accounts for much variation in the height and duration of the R in V_1. In others, it has little effect. These findings are discussed in relation to published criteria for the diagnosis of right ventricular hypertrophy.

The QRS loop has been studied in these individuals and a generalization is attempted. A discussion of the problems of spatial vectorcardiography in infants leads to the conclusion that the newer accurate methods are likely to break down when applied to infants.

The evolution of the changes which occur in the T wave and ventricular gradient are correlated with the evolution of the changes which occur in the QRS loop.

Incidence and Mortality Rates of Forty-four Various Entities of Congenital Malformations of the Heart: A Nine-Year Study of 1,464 Patients

Benjamin M. Gasul, Egbert H. Fell, Robert F. Dillon, Paul Szanto, and Vlastimil Vrla, Chicago, Ill.

Until recently the data on the incidence of various types of congenital malformations of the heart in infants and children were based primarily on autopsy findings. Our data are the result of a correlative study of the physical, fluoroscopic, roentgenologic and electrocardiographic findings with those obtained from angiocardiography, cardiac catheterization, the operating room experiences and autopsy findings.

The diagnosis was confirmed by autopsy in 430 cases, cardiac catheterization in 505, angiocardiography 875, phonocardiography in 550 and surgery in 355 patients.

Of the 44 different entities encountered in this study, the following 7 types are the most frequent cases: Ventricular septal defect, 313 patients (21.3 per cent); atrial septal defects (includes ostium secundum, ostium primum and A-V valves), 780 patients (12.3 per cent); tetralogy of Fallot (includes pseudotruncus arteriosus and pentalogy), 169 patients (11.5 per cent); patent ductus arteriosus, 149 patients (10.2 per cent); pulmonary stenosis with normal aortic root (includes: with atrial septal defect, ventricular septal defect and pulmonary atresia), 90 patients (6.7 per cent); coarctation of the aorta, post ductal, adult type, 57 patients; preductal, infantile type, 22 patients (together 5.4 per cent); transposition of the great vessels, 61 patients (4.2 per cent). These 7 types represent 71.6 per cent of the total number of patients studied.

Of the 430 autopsies, 339 or 78 per cent were performed on patients under 1 year of age. The following 7 entities account for 205 of these autopsies: tetralogy of Fallot, atrial septal defect, transposition of the great vessels, ventricular septal defect, tricuspid atresia and stenosis, coarctation of the aorta, and pulmonary stenosis or atresia with normal aortic root.

It is important to point out that there were no deaths in patients with ventricular septal defects between the ages of 1 and 15 years, and that the total death rate of this entity was 10 per cent. The mortality rate during the first year of life in infants with complete transposition of the great vessels was 93.3 per cent.

Tables will present the incidence and the mortality rates of the other 37 entities.

Water and Electrolyte Exchanges Between Excised Tissues and Plasma

Mario Gaudino,† New York, N. Y.

Freshly excised rabbit tissues did not maintain their water and electrolyte composition when immersed in vitro in plasma obtained from blood of the same animal. All gained water, chloride and sodium and, in general, lost potassium. Changes occurred with varying speed and degree for each tissue. Increases in skin appeared to be due to entrance of plasma or plasma filtrate. In tendon there were indications of a selective water imbibition, although similarities existed with skin changes. In muscle, liver and brain, chloride and sodium entered in larger proportion than explained by a plasma filtrate entrance. More sodium entered than potassium was lost with a resulting cation gain. In muscle and liver there was some evidence that sodium gain in excess of potassium lost could have been due to plasma or plasma filtrate entrance. In brain, all water and electrolyte movements seemed to be independent of each other. A relatively large proportion of the potassium content of muscle seemed to be readily exchangeable with plasma. The opposite was true for liver and brain. Control chloride and sodium tissue spaces of skin and tendon in most instances were greater than total water, a fact which made calculations of spaces of doubtful value for determining cellular and interstitial tissue fractions. Different sizes of radioactive sucrose, chloride and sodium spaces in muscle, liver and brain left the question of which was a true indicator of extracellular volume unanswered. Endogenous reductase activity measured with a tetrazolium salt was fairly well maintained after immersion in all tissues except brain, but no relationship between this activity and electrolyte composition could be ascertained. No activity was detected in tendon.

Pressure Pulses in the Right Ventricle and Pulmonary Artery in Valvular Pulmonary Stenosis

Gabriel Genkins, Howard L. Moscovitz, and Alvin J. Gordon, New York, N. Y.

In 10 patients with valvular pulmonary stenosis and normal aortic root, simultaneous, equisensitive pressure pulses were obtained in the exposed heart by needle puncture before and after transventricular valvulotomy.

A characteristically peaked right ventricular pulse contour was found in all cases. This was related to a marked diminution in the duration of the isometric contraction and relaxation periods and a relatively steady rate of ejection through an unchanging pulmonary orifice.

The pressure pulse in the pulmonary artery was flat in the most severe cases, but the normal features of an arterial tracing could be identified in the milder forms. An early systolic dip was present in half of the cases. In an equal number, the pulmonary artery diastolic pressure approached the right ventricular diastolic pressures. Together with the absence of a dicrotic notch, this fact suggests that the deformed valves were not only stenotic but incompetent.

The maximum right ventricular systolic pressure values averaged 100 mm. Hg in the 10 patients, and the pulmonary artery mean pressures averaged 19 mm. Hg. The mean systolic ejection gradient averaged 52 mm. Hg. Following valvulotomy the average maximum of the right ventricular pressures dropped to 68 mm. Hg, the mean pulmonary pressure rose to 24 mm. Hg, and the gradient fell to 27 mm. Hg.

This method of hemodynamic investigation has been found to be superior in many ways to cardiac catheterization in this condition. The cardiac cycle and the relationships between electric and mechanical events in valvular pulmonary stenosis will be analyzed by reference to characteristic tracings.

Cardiac Myosin

John Gergely,† Mary A. Gouvea, and Heinz Kohler, Boston, Mass.

Crystalline, actin-free, myosin was prepared from dog and beef heart by extraction with KCl-pyrophosphate, actin was removed by ultracentrifugation and precipitation at an ionic strength of 0.3, and the myosin crystallized 4 times at an ionic strength of 0.06. The molecular weight was determined by diffusion-sedimentation, and by light scattering measurements at angles ranging from 25° to 135°. These methods yield values of 850,000 ± 10 per cent. The length of the myosin molecule, derived from light scattering measurements accord-

ng to Zimm, is 1200–1700 Å, depending on whether ne considers it as a random coil or as a stiff rod. Measurements of double refraction of flow give a ength of about 1700 Å. (The value for skeletal nyosin is 1600 Å.) The ATPase activity of cardiac nyosin is stimulated by Ca, inhibited by Mg ions. The Q_P value is 1000–1200, measured at 38°, pH 0.1, in 10^{-2}M Ca. The intrinsic viscosity, extrapolated to 0 concentration is 1.9–2.0, corresponding o an axial ratio of 65–70. Thus, the physicochemical characteristics of heart myosin seem to be very lose to those of rabbit skeletal myosin, but the enzymatic activity is about 3 times lower than that of the skeletal protein. The physicochemical characteristics do not seem to vary with the species, or, within reasonable limits, with the time elapsed between killing the animal and removing the heart. Our results appear to be at variance with those of Stern, Ellenbogen, and Olson (Fed. Proc. **15:** 764, 1956), whose preparations have a much lower Q_P value, and seem to consist of smaller molecules.

Corrected Transposition of the Great Vessels with Pulmonary Stenosis

James E. Gibbons, George L. Donnelly, Jerome S. Harris, and Edward S. Orgain, Durham, N. C.

When isolated situs inversus of the bulboventricular loop exists in situs solitus, limitation of counterclockwise torsion of the truncus septum to 45 degrees brings the origin of the aorta to a left anterior position and the pulmonary artery to a right posterior position. Thus, in this rare syndrome of corrected transposition, the 2 serious anomalies of partial inversion of the ventricles and transposition of the great vessels neutralize each other. Nevertheless, associated cardiac anomalies are very frequent, especially septal defects and deformities of the left atrial ventricular valve. Only 1 instance of complicating pulmonary stenosis has been reported.

Catheterization data and operative findings will be presented on 3 patients with corrected transposition complicated by pulmonary stenosis. Two patients presented with suspected isolated pulmonary stenosis and 1 with tetralogy of Fallot. The complex nature of the malformation was recognized only at operation where transventricular pulmonary valvulotomy could not be performed because of the anomalous position of the pulmonary artery.

Accurate differentiation of this syndrome from isolated pulmonary stenosis or tetralogy of Fallot has not been possible from physical findings and routine x-rays. However, the electrocardiogram is considered to be extremely valuable diagnostically. In every case the mean QRS vector was directed to the right in the frontal plane, but quite posterior in space. The deep S waves in the right and mid-precordial leads indicated hypertrophy of the posterior ventricle. It is suggested that when this electrocardiographic picture is seen in suspected pulmonary stenosis or tetralogy of Fallot, the syndrome of corrected transposition of the great vessels should be suspected.

Raynaud's Disease Among Women: A Clinical and Follow-up Study

Ray W. Gifford, Jr. and Edgar A. Hines, Jr., Rochester, Minn.

The diagnosis of Raynaud's disease was made or suspected in 756 women at the Mayo Clinic from 1920 through 1945. When these diagnoses were revised according to the criteria of Allen and Brown, the original diagnosis of Raynaud's disease was considered incorrect in 127 instances and questionable in 252 instances. Follow-up information was available on 208 of the 252 women who had questionable diagnoses and it revealed that 53 per cent actually did have Raynaud's disease. The subsequent course of the remaining 47 per cent, who were found to have secondary Raynaud's phenomenon, will be presented. As a result of our revision of diagnoses, the original diagnosis of Raynaud's disease was confirmed in 377 instances. This diagnosis was substantiated for 267 (95 per cent) of the 280 women on whom we were able to obtain follow-up information.

Review of the records of 474 women who had timeproved Raynaud's disease and of follow-up information obtained on 307 women who were treated conservatively confirms the benignancy of the usual form of this disease. No deaths were attributed to it, and very little disability resulted. Amputation of terminal phalanges for complications of Raynaud's disease was necessary for only 0.4 per cent of the patients before coming to the clinic and for none during the period of follow-up. Raynaud's phenomenon became less troublesome or disappeared in 46 per cent of the patients. Trophic lesions of the fingers and sclerodactylia improved or disappeared in the majority of women who had these complications. Major amputations were not necessary and gangrene did not occur in any instances. Not included in this follow-up of treatment are 70 patients who had sympathectomy and who had, on an average, more severe symptoms and complications before treatment was instituted than did the group who were treated conservatively.

Sympathectomy For Raynaud's Phenomenon: Follow-up Study of Seventy Women with Raynaud's Disease and Fifty-Four Women with Secondary Raynaud's Phenomenon

Ray W. Gifford, Jr., Edgar A. Hines, Jr., and Winchell McK. Craig, Rochester, Minn.

In another communication, Gifford and Hines reviewed the clinical data on 474 women for whom a diagnosis of Raynaud's disease had been confirmed by application of the criteria of Allen and Brown. A

total of 77 women with Raynaud's disease were subjected to surgical sympathetic denervation of 1 extremity or more; adequate follow-up information was obtained on 70 of these patients. Two of the patients with Raynaud's disease had sympathectomy for the lower extremities only. Sympathectomy for the upper extremities gave good or excellent results for 37 (55 per cent) of 68 women with Raynaud's disease. Results were considered good or excellent only if the effect of the sympathectomy persisted throughout the period of follow-up. Good or excellent results were obtained in 68 per cent if complications of Raynaud's disease (trophic lesions or sclerodactylia or both) were not present before operation. Significant differences did not exist between the results regardless of whether the sympathectomy was preganglionic or postganglionic. Two (3 per cent) of the 68 patients lost portions of 1 or more fingers after sympathectomy. In the group who did not obtain good or excellent results, a great tendency to relapse was noted during the first 2 years after sympathectomy.

Sympathectomy for the lower extremities gave excellent results for 17 (95 per cent) of 18 women who had Raynaud's disease.

Follow-up information was obtained on 54 women with Raynaud's phenomenon secondary to other diseases who were subjected to sympathectomy of the upper or lower extremities, or both, prior to 1946. Sympathectomy gave poor results in the upper extremities in 72 per cent of these patients; results in the lower extremities were only slightly better.

Transarterial Pulmonary Valvulotomy in the Functioning Heart: A Digital and Instrumental Approach Through a Diverticulum

William W. L. Glenn, Herbert S. Harned, Jr., and Allan V. N. Goodyer,† New Haven, Conn.

A total of 28 patients with the diagnosis of pulmonary valvular stenosis ranging in age from 3 to 46 years have been operated upon by our group. In 15 of these patients the valvulotomy was performed through the anterior wall of the right ventricle and in 12 valvulotomy was accomplished through a rubber or rubberized nylon diverticulum sewed to an incision in the wall of the main pulmonary artery. In 1 additional patient, age 38, where the transarterial approach was employed, no pulmonary valvular stenosis was found, but both a subvalvular stenosis due to a thin membrane and a tight infundibular stenosis which would barely admit the tip of the valvulotome were relieved.

In all cases the heart was functioning at the time of valvulotomy. There was 1 death, a 46-year-old patient died on the sixth postoperative day.

Cardiac catheterization was carried out preoperatively in all patients but 1, and postoperative catheterization data will be available in most of the patients where the transventricular approach was employed. From the studies performed thus far, it would appear that a superior valvulotomy can be obtained through a diverticulum sutured to the pulmonary artery. The gradient from the right ventricle to the pulmonary artery may not be abolished completely and there is some evidence from the catheterization data that some pulmonary insufficiency may be produced, although this is not necessarily evident by auscultation.

The chief advantage of the transarterial digital approach to the pulmonary valve in the functioning heart is that it permits a prolonged deliberate palpation of the artery, the valve, and the right ventricular chamber with the institution of carefully directed corrective surgical technics with minimal risk to the patient. This approach would appear to be indicated especially in older children and adults with pulmonary stenosis.

This approach to the pulmonary valve in the older age groups is not as great a risk as the visual approach at the present time. Also, the surgical technic and the results are superior to the blind instrumental approach through the right ventricle.

Estimation of the Severity of Aortic Stenosis by Combined Heart Catheterization

Harry Goldberg, Ralph Smith, and George Raber, Philadelphia, Pa.

The need for accurate assessment of the degree of aortic stenosis is evidenced by presently employed surgical relief of this lesion. Simultaneous left and right heart catheterization allows for direct measurement of the pressure gradient and flow. The stenosis thus can be estimated more accurately than previously.

Thirty-six patients with pure aortic stenosis were studied. The cardiac index was low, averaging 2.2 L./min./M.^{2} (range: 1.0–3.4 L./min./M.^{2}). The pressure gradient, averaging 55 mm. Hg by planimetry (range: 28–94 mm. Hg) alone was not an accurate index of the degree of obstruction. The aortic valve area averaged 0.5 cm.^{2} (range: 0.2–1.1 cm.^{2}). There was generally good agreement between the calculated area and that found at surgery (33 cases), or autopsy (1 case).

The diastolic pressure in the left ventricle was generally elevated and did not correlate with the presence of clinical left ventricular failure. The high diastolic pressure is attributed to alteration in the pressure-volume relationships of the left ventricle secondary to hypertrophy. There was no constant relationship between the stroke volume, pressure gradient, or valve area and the position of the anacrotic notch or time to peak of systole in the brachial artery pressure tracing.

Fourteen patients were re-evaluated following transaortic commissurotomy. The aortic flow increased in 9, decreased in 3, and was unchanged in 2. The left ventricular systolic pressure decreased in all but 3. The diastolic pressure changed little. In 2 cases the gradient was eliminated by the surgery.

In the remaining, it fell a variable amount (5–45 mm. Hg). The valve area was increased in 11 patients; no change in 3. Residual stenosis is attributed to extreme calcification of aortic leaflets, and failure of the surgeon to open all 3 commissures.

This data confirms the necessity of a knowledge of flow as well as gradient in defining the degree of aortic obstruction and in evaluating the results of surgery.

Clinical Application of Simultaneous Equisensitive Recording of Pressure Pulses in the Exposed Human Heart

Alvin J. Gordon, Richard P. Lasser, Leslie A. Kuhn, Howard L. Moscovitz, Samuel O. Sapin, James B. Minor, and Gabriel Genkins, New York, N. Y.

The method of obtaining up to 3 simultaneous pressure pulses on the human heart exposed during surgery, has been described previously. By adjusting the pressure transducers to equal sensitivity, and using identical 0 points, the tracings are superimposed and displayed in relation to each other. They may either be visualized directly on an oscilloscopic screen or recorded photographically. In this way the mechanical events of the cardiac cycle may be measured with precision and their temporal relationship with the simultaneously inscribed electrocardiogram noted. The cross-over points on the curves identify opening and closing of valves. Gradients across stenotic valves are readily apparent, and changes brought about by operative correction evaluated immediately, as an aid to the surgeon. By recording sounds from the exposed heart simultaneously with the pressure pulses, the technic lends itself to accurate study of the genesis of heart sounds and murmurs.

Pressure pulses will be demonstrated from the normal human heart, both left and right side. Representative tracings from cases of mitral stenosis will be shown, with emphasis on the mean atrioventricular filling pressure gradient, which averaged 13 mm. Hg in a series of 8 cases. This gradient was observed to fall to a variable extent after commissurotomy.

In the case of tricuspid stenosis the mean atrioventricular filling pressure gradient amounted to 6 mm. Hg, although by the end of diastole (Z point) the gradient had been eliminated, presumably by vigorous right atrial contraction.

The hemodynamics of patent ductus arteriosus, with and without pulmonary hypertension, and of valvular pulmonary stenosis will be demonstrated.

Potassium and Cardiac Damage in Renal Hypertension

David B. Gordon, Los Angeles, Calif., and Kenneth Barrett, London, England.*

Potassium, in the form of 1 per cent potassium chloride solution, was given as the sole drinking fluid to male rabbits with experimental renal hypertension. Similar rabbits were kept on tap water as controls. Contrary to our previous findings (in female rabbits) there was no difference in the incidence of hemorrhages of the gut in the 2 groups. However, there were differences between the 2 groups in that the animals given potassium survived longer and there was a much lower incidence of interstitial hemorrhage in the heart muscle of the animals given potassium.

The potassium content of the right and left ventricles was measured and it was found that in the hypertensive animals the concentration was somewhat lower in the right ventricular muscle than in the left, although not necessarily lower than the range of potassium concentration in normal rabbit hearts. It was also found that where myocardial hemorrhage occurred it was always more severe in the right ventricle (and atrium than in the left.

Transcoronary Circulation Time: A New Method of Evaluating the Coronary Vascular System

Richard Gorlin and John P. Storaasli, Portsmouth, Va.

The current methods of studying the coronary circulation in man are limited by the long period of time and the excessive removal of blood necessary for each determination. Both limitations have been obviated by a new radioisotope technic which gives circulation time through the coronary vascular system draining the left ventricle. A scintillation counter, with little collimation, is located over the anterior thorax usually to the left of the midline between the third and fifth interspaces. A standard cardiac catheter is located in the coronary sinus. Radioactive iodinated serum albumin is injected into an arm vein. Its arrival over the right and left heart chambers is detected by the surface counter from which a typical 2 humped radiocardiographic curve is written. The isotope is next detected from the catheter, either via multiple syringe sampling, or continuous sampling past a second scintillation counter. Transcoronary circulation time (TCT) is measured from arrival over the left heart to arrival at the catheter (corrected for delay in withdrawal).

In 15 normals and patients with mild heart disease, TCT varied from 6.5 to 11 sec. Nitroglycerin, exercise, and atropine cardioacceleration decreased this time, while Valsalva's maneuver increased it. In all cases where TCT decreased, the simultaneously measured coronary blood flow by the nitrous oxide technic increased. The direct relation of increase in velocity with increase in flow would suggest that all rather than part of the coronary vascular bed is functioning at rest and simply dilates in response to demand. The method is offered as a rapid means of evaluating coronary circulatory changes in a given patient.

Peri-infarction Block as a Cause of Left Axis Deviation

Robert P. Grant, Bethesda, Md.

It has been shown previously that in 50 per cent of cases of anterolateral infarction (as defined by initial QRS force deformity) there is also a characteristic and diagnostic deformity of the terminal part of the QRS complex in all leads of the conventional clinical tracing. This terminal deformity is due to an alteration in the direction of the last forces generated during the QRS interval. When plotted on the triaxial reference figure they tend to be opposite in direction to the initial QRS forces, those responsible for "Q waves." The terminal force abnormality is believed to be due to a conduction defect in the region of the myocardium overlying the infarct and for that reason is called peri-infarction block, whether or not associated with prolongation of the QRS interval.

Since the terminal QRS forces of anterolateral peri-infarction block are directed leftward and superiorly, they resemble the direction of QRS forces in marked left axis deviation, and differentiating this syndrome from simple left axis deviation is therefore of importance to the clinical electrocardiographer. In an electrocardiographic-pathologic survey of 672 consecutive cases with the conventional twelve-lead ECG within 5 weeks of death (circulation **14:** 233, 1956), there were 131 cases of marked left axis deviation, over a third of whom had myocardial infarction at autopsy. The majority of these were examples of anterolateral peri-infarction block, and it was found that the left axis deviation of anterolateral peri-infarction block could be differentiated from other causes of left axis deviation in all cases by the angle between the initial and terminal QRS forces as plotted from the conventional clinical tracing. Indeed, there were 4 cases with infarction and no other abnormality at autopsy in whom this vector criterion was fulfilled, but in whom there were no diagnostic "Q waves" on any of the conventional leads.

It is concluded that peri-infarction block is an important cause of left axis deviation and that current "pattern" criteria are inadequate for identifying many of these cases. The study also illustrates a useful application of vector methods in the interpretation of the conventional clinical tracing.

Hemodynamic and Volumetric Changes in Mitral Valve Disease in Man

Robert P. Grant, Andrew G. Morrow, and Edward Sharpe, Bethesda, Md.

In 65 consecutive patients with mitral valve disease, right heart catheterization by the conventional method, left heart catheterization by the transbronchial method, and rapid biplane angiocardiography have been performed making possible a comprehensive correlation of hemodynamic and volumetric changes in the right and left sides of the heart in these patients.

Increases in left atrial volume beyond 500 ml. tended to be associated with progressively greater degrees of left atrial hemodynamic evidence of mitral insufficiency. This was particularly true when the mitral valve disease had been due to rheumatic fever; other structural and hemodynamic differences between this and other etiologies of mitral insufficiency are discussed. In 6 patients with mitral valve disease due to rheumatic fever, the left atrial volume exceeded 1 L. The clinical picture of the giant left atrial syndrome is found to be due to the predominating mitral insufficiency. Evidence is presented suggesting that rheumatic mitral insufficiency has from its inception a different and distinguishable clinical evolution from that of mitral stenosis.

In 5 cases, associated aortic valve disease or arterial hypertension participated in converting what appeared to have been predominating mitral stenosis into the clinical and hemodynamic picture of predominating mitral insufficiency; in 2 of these the remediable nature of the underlying valvular disease was obscured by the mitral insufficiency.

The relationship between the hemodynamic changes and other volumetric features such as the pulmonary artery diameter, elongation of the right ventricle, and left ventricular size in these cases are also discussed.

Responsiveness of Vasomotor Receptors in Major Vascular Beds

Harold D. Green and Adam B. Denison, Jr., Winston-Salem, N. C.

Control of arterioles in the major vascular beds has been studied by metering arterial inflow (electromagnetic meter) and pressure (strain gage), while stimulating the appropriate anatomic nerves, or injecting the appropriate mediator intra-arterially. Both epinephrine and arterenol caused vasoconstriction in the cutaneous, mesenteric, skeletal muscle, renal and hepatic (artery and vein) beds but not in the coronary (myocardium) or internal carotid (cerebrum) beds. Isopropylarterenol, and epinephrine, after moderate adrenergic blockage, induced vasodilation which was greatest in skeletal muscle and the intestinal "gut" circuit, and was moderated in the myocardial circuit but was absent in the renal, hepatic and cerebral circuits and almost absent in skin. Dilator responses to cholinergic stimulation (methacholine) were clearly demonstrated only in skeletal muscle.

Evidence of adrenergic autonomic nerve vasoconstrictor regulation was demonstrated for all organs except the heart and brain. In every case arterenol mimicked the responses to nerve stimulation more closely than did epinephrine. With the exception of the heart (where arterenol caused vaso-

dilation) no evidence for the presence of adrenergically mediated vasodilator autonomic nerve fibers was found. Cholinergically mediated, autonomic nerve fibers were demonstrated only for skeletal muscle. Vasodilation in response to ischemia was prominent in the heart and skeletal muscle but was practically absent from cutaneous, splanchnic and cerebral beds.

Conclusions. In instances of impaired myocardial or cerebral blood flow due to arterial hypotension, widespread sympathetic vasoconstrictor nerve activity or infusion of arterenol would appear to be superior to infusion of epinephrine, because of the tendency of the latter to cause vasodilation in skeletal muscle and the gut. The cardiovascular significance of the dual (dilator-constrictor) activity of epinephrine in skeletal muscle and the gut remains obscure.

Pressor and Depressor Responses to Tilting in Hypertensive Patients

Robert S. Green, Arnold Iglauer, and Ralph C. Scott, Cincinnati, Ohio.

The responses of intra-arterial blood pressure to passive head-up and head-down tilting have been obtained for 50 patients with well-established hypertension, and compared with results obtained for 20 subjects with normal cardiovascular systems.

A normal depressor response following head-down tilting, and a normal pressor response following head-up tilting, occurred together in 11 patients. Variations from the normal pattern were noted in 39 patients in whom either or both responses were increased, decreased or absent.

The independence of depressor and pressor responses was demonstrated and evidence obtained that these responses were mediated by a neural mechanism.

The data suggest that dysfunction of the reflex depressor "buffer mechanism" as well as of reflex pressor mechanism may be important in the etiology and/or the progress of hypertension in a given patient. Depressor activity was diminished or absent in 26 patients.

Increased depressor activity in the head-down position was obtained invariably in patients who complained of dizziness with bending over, and decreased or absent pressor activity in the erect position was obtained in patients who had dizziness on arising.

Effect of Molar Sodium Lactate on the Tolerance to Potassium in Nephrectomized Dogs

Sidney Greenstein, Warren P. Goldburgh, Santiago V. Guzman, and Samuel Bellet, Philadelphia, Pa.

Because of the demonstrated efficacy of molar sodium lactate (Bellet and associates) in the treatment of hyperkalemic patients, the following experiments were performed to elucidate its mechanism of action. Sixteen nephrectomized dogs were continuously infused with potassium chloride at a constant rate, with continuous electrocardiographic monitoring and intermittent arterial blood sampling for electrolytes, pH, and lactic acid. Nine dogs were treated 26 times with molar sodium lactate administered rapidly intravenously. Changes in potassium partition and kinetics, serum electrolytes and pH, extracellular volume and electrocardiographic signs of hyperkalemia were analyzed and correlated. In 19 of the 26 trials, rapid, marked, and sustained electrocardiographic improvement occurred, associated with significant falls in extracellular potassium and potassium concentration and increased rate of potassium transfer intracellularly, in spite of continuous potassium infusion. Increase in extracellular sodium, pH, and lactate were noted.

In 32 additional dogs, molar sodium lactate, sodium bicarbonate, sodium chloride, glucose and insulin, and calcium gluconate were compared under the above conditions as to their relative effect on electrocardiographic improvements, potassium partition, and extracellular electrolytes, pH, and volume.

Molar sodium lactate was superior in regards to electrocardiographic improvement and protection against potassium cardiotoxicity. It was the only agent that maintained its effectiveness in successive treatments. It produced a gradual pH rise and the least rise in extracellular sodium of the sodium salts used. Sodium bicarbonate produced the greatest pH rise, decrease in extracellular potassium, increase in intracellular potassium transfer with significantly less electrocardiographic improvement, and the greatest number of treatment failures. Glucose-insulin produced significant increases in intracellular potassium transfer, but produced less electrocardiographic improvement, and was associated with falls in extracellular sodium and pH. Sodium chloride and calcium gluconate were considerably less effective in producing electrocardiographic improvement and favorable potassium partition. The results of these experiments would suggest that molar sodium lactate is the agent of choice in the treatment of acute hyperkalemic cardiotoxicity.

Congenital Pulmonary Atresia With Intact Ventricular Septum: Two Anatomic Types

Warren E. Greenwold, James W. DuShane, Howard B. Burchell, Andre Bruwer, and Jesse E Edwards, Rochester, Minn.

The majority of reports describing congenital pulmonary atresia with intact ventricular septum stress the extremely small right ventricular chamber. The implications regarding prognosis after relief of the pulmonary valvular obstruction in such cases are necessarily pessimistic. The tiny right ventricle represents not only an inadequate pump but an

impediment to the flow of blood through the right heart. We wish to emphasize another type of heart with pulmonary atresia; in this type, the right ventricular chamber is of normal size or even larger. Thus, in this second type of case, one might expect good results after removal of the pulmonary valvular obstruction.

This report is based on 12 cases; the right ventricle was small in 6 cases, whereas it was large in the remaining 6. Death occurred in infancy in all patients.

Clinically, cyanosis was common and early. Electrocardiographic and roentgenographic features allow distinction of the 2 types. In the presence of a small right ventricle, the size of the heart is not increased roentgenologically and there may be convexity at the pulmonary artery. With a large or normal-sized right ventricle, roentgenologic evidence of pronounced cardiac enlargement is present and the transverse diameter of the heart is greatly increased because of enlargement of the right ventricle and striking enlargement of the right atrium.

Electrocardiographically, the patients with small right ventricular chambers show evidence of left ventricular diastolic overload, left atrial enlargement and left axis deviation. Patients with normal-sized or large right ventricular chambers show right ventricular systolic overload, right atrial enlargement and right axis deviation. The latter patients also show evidence of increased left ventricular work when they survive for several weeks after birth.

It is important to differentiate these 2 types of patients with pulmonary atresia and intact ventricular septum because it is hoped that benefits may be derived from surgical correction done on those patients who have normal-sized or large right ventricular chambers.

Effect of Background Noise on Auscultation of Murmurs

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It is axiomatic that to hear a faint cardiac murmur one should listen in a quiet environment. The masking effect of background noise on auscultatory hearing is well known to clinicians, but perhaps less well known is the degree to which this can impair one's ability to hear low intensity murmurs such as those produced by early valvular heart disease. The purpose of this study was to measure the degree of this impairment under conditions simulating those of ordinary cardiac auscultation. Two types of measurements were utilized:

1. Those of the ambient background noise levels in hospital wards and examining rooms of a typical medical center. These were found to be far higher than might be supposed, ranging from 55 to 75 decibels.

2. The auscultatory threshold for a heart murmur in a soundproofed room having a background noise level of 35 decibels, and again under conditions of ordinary noise. Forty physicians served as subjects for the experiment. With their stethoscopes they listened to a diastolic murmur reproduced at variable intensity in an "artificial precordium," a water-filled plastic bag approximating the acoustical characteristics of flesh.

All subjects showed a marked difference in their ability to hear the murmur with and without the usual background noise. Average difference for the 40 physicians was 11.8 decibels; this means that the murmur had to be increased to more than 12 times the intensity of that audible in the quiet environment before it could be heard in the presence of ordinary examining room noise.

It is concluded that: 1. The surprisingly high levels of ambient noise to which we have become acclimated in hospital wards and examining rooms are not conducive to accurate auscultatory examination of the heart. 2. While age, experience, hearing acuity, and stethoscope characteristics doubtless all play a role, the level of background noise in the examining room constitutes a major factor in determining one's ability to detect a murmur.

Intravenous Calcium in Acute Pulmonary Edema

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Calcium gluconate, in dosage of 1 Gm. intravenously, has a rapid and striking effect in augmenting the force of cardiac contraction. In 10 nondigitalized cardiac patients whose control velocity ballistocardiograms were abnormal, I and J waves increased in amplitude, and respiratory variation decreased within 1 to 2 min. after giving calcium. With acetyl-strophanthidin (3-cat units) these changes were less marked and first appeared 7 to 10 min. after intravenous injection.

Calcium gluconate has been successfully administered as the sole therapeutic measure in 7 consecutive patients with severe acute pulmonary edema due to hypertensive heart disease and acute myocardial infarction. The initial dose of calcium served as a test of circulation time, which averaged 26 sec. Six to 21 min. later (average 16 min.) a second 1 Gm. dose of calcium gluconate was given. Within this brief period the circulation time fell from 26 to 16 sec., with a significant decrease in each instance.

Other subjective and objective indications of improvement appeared almost immediately after the initial dose of calcium. Within 2 min. pulse pressure increased 74 per cent reflecting an increased stroke output, and the heart rate slowed 20 points from an average of 109 to 89/min. Cyanosis, tachypnea, and wheezing disappeared promptly, and rales, which initially were audible throughout both lung fields,

cleared within 5 to 10 min. leaving no or only a few residual basal rales. There was accompanying subjective relief, increased comfort and allaying of anxiety. One patient with pulmonary edema due to acute myocardial infarction, who had received ¼ gr. morphine and 0.5 Gm. aminophylline intravenously 1 hour previously without any benefit, improved strikingly after calcium.

Intravenous calcium gluconate is a potent agent in acute pulmonary edema, augmenting, almost instantly, the force of the failing heart. Since its action is brief, digitalis may be administered immediately after relief has been obtained, to maintain cardiac compensation.

Survey of Electrocardiographic Practice in the United States

Richard S. Gubner and Harry E. Ungerleider, New York, N. Y.

Material for this study comprised 500 consecutive electrocardiograms (representing as many physicians and all sections of the nation) made on insurance applicants who had had recent medical attention including an electrocardiogram.

Among 206 persons in whom electrocardiograms were taken during routine examinations, significant abnormalities were present in 10, minor or borderline changes in 9. No major abnormalities occurred among 121 below the age of 45. Other reasons for study included: chest pain (99); other symptoms, signs or history of a heart disorder (87); noncardiac symptoms (108).

Eighty per cent of electrocardiograms were recorded with direct writing instruments, 20 per cent with photographic machines. Of the entire 500, 12 lead tracings (1, 2, 3, aVr-1-f-, V_{1-6}) were made in 70 per cent. Exercise tests for coronary insufficiency were performed in 13 of the 99 complaining of chest pain.

Serious technical errors were made in 13 of the 500 tracings, leading to the erroneous diagnosis of coronary occlusion in 3 instances.

In 24 of the 500 cases an erroneous diagnosis of heart disease was made on normal electrocardiograms. These included 10 cases diagnosed as coronary occlusion, 7 diagnosed as left ventricular hypertrophy, and 7 with miscellaneous spurious diagnoses. Ninety-one of the 500 electrocardiograms were abnormal. In 40 abnormalities present were not recognized. These included 20 with abnormal QRS complexes (significant Q waves, bundle block, WPW pattern) and T wave changes. Also unrecognized were 12 cases with a high voltage pattern indicating left ventricular hypertrophy (all had additional evidence of heart disease), 3 with evidence of atrial hypertrophy, and 3 with prolonged A-V conduction. In 2 instances with typical patterns of acute pericarditis a diagnosis of coronary occlusion was made.

Errors of commission and omission in electrocardiographic technic and interpretation are common, notably failure to standardize, and failure to recognize early patterns of chamber hypertrophy. Exercise tests are too infrequently performed, and technics and interpretation vary widely. Routine electrocardiograms are of little or no value below the age of 45.

Increase in Myocardial Contractility as a Factor in the Treatment of Cardiogenic Shock

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It has been proposed that the ideal vasopressor agent for the treatment of shock after an acute myocardial infarction would be 1 which would elevate arterial pressure solely by increasing peripheral vascular resistance. The experiments to be presented suggest that augmentation of myocardial contractility is an important factor in correcting the hypotension in this condition.

The hemodynamic responses of norepinephrine and methoxamine were studied in dogs with hypotension after occlusion of 1 of the main branches of the left coronary artery, or its partial obstruction by lycopodium spore emboli. These pressor amines were selected for this study because norepinephrine has been shown to increase myocardial contractility while methoxamine lacks this effect. Myocardial contractility was measured by means of a Walton strain gage attached to the anterior surface of the left ventricle. The left coronary artery was catheterized through 1 of the carotid arteries for intracoronary injections.

Coronary arterial injections of norepinephrine (0.02–0.04 μg./Kg.) resulted in an immediate increase in strength of myocardial contraction, rise in peripheral arterial pressure of approximately 40 mm. Hg and a fall in left atrial mean pressure of approximately 5 mm. Hg. Intracoronary injections of methoxamine (4 to 8 μg./Kg.) neither increased strength of myocardial contraction nor elevated the systemic arterial pressure, while left atrial pressure either increased or remained unchanged.

Intravenous injections of norepinephrine resulted in an elevation of arterial pressure and a fall in left atrial pressure. Methoxamine similarly raised the systemic arterial pressure but the mean left atrial pressure became markedly elevated.

These studies suggest that increasing the force of myocardial contraction alone can significantly elevate arterial blood pressure in a hypotensive state secondary to coronary obstruction. They also show that although the hypotension produced by myocardial infarction is alleviated by intravenous injection of norepinephrine or methoxamine, the fact that the left atrial pressure dropped after norepinephrine but rose after methoxamine injection strongly suggest that a drug which increases myocardial contractility and peripheral vascular re-

sistance may be a more effective agent in the treatment of a shock-like state produced by coronary occlusion.

Influence of Retained Pericardial Blood on Postoperative Reactions in Man

Leonard P. Haber, John J. Sampson, and Sanford E. Leeds, San Francisco, Calif.

Mechanisms of acute local and systemic reactions to surgical operative procedures on the heart are not clearly understood. Included in the group of such reactions is the "postcommissurotomy syndrome," which is believed by some investigators to represent a pericarditis induced by trauma and possibly by the presence of blood in the pericardial cavity.

Five successive cases, 3 of which were rheumatic mitral stenosis, were studied in which the pericardium was entered for performance of operative procedure on the heart. Four of these had approximately 50 ml. of blood purposely introduced into the pericardial cavity which was then closed. The fifth case was meticulously freed of free fluid or blood prior to closure.

The cases were studied by daily electrocardiograms for 7 days, alternate days for 2 weeks and frequently thereafter to time of discharge. Antistreptolysin titer and C-reactive protein content of the serum, erythrocyte sedimentation rate, blood count, chest x-rays and clinical observations including fever, pain and cardiac arrhythmias were obtained throughout the postoperative course.

Three of the 4 cases in which blood was left in the pericardium showed electrocardiographic evidence of pericarditis by initial S-T segment elevation and persistent T wave inversion for 8 to 29 days. The fourth case exhibited no postoperative electrocardiographic abnormality.

The fifth case, rheumatic mitral stenosis, freed of immediate pericardial fluid and blood. developed electrocardiographic evidence of pericarditis promptly, improved but relapsed with pain and other features suggesting "postoperative commissurotomy syndrome" from the twelfth to the twenty-third postoperative day. In no case was there evidence of rheumatic activity from elevation of antistreptolysin titer or C-reactive protein content of the serum.

The conclusions are that immediately retained blood in the pericardium in modest amounts does not initiate the persistent pericarditis or the clinical pattern of postoperative "commissurotomy syndrome." The influence of later bleeding or fluid accumulation in the pericardial sac cannot be ascertained from this report.

Studies in Differential Vectorcardiography of the Dog. I. QRS Vectorcardiogram of the Normal Dog

Robert L. Hamlin and Herman K. Hellerstein, Cleveland, Ohio.

This report is the first in the literature presenting: (1) the isolated spatial QRS vectorcardiogram of the normal dog, (2) correlation between the vectorcardiogram and the electrocardiogram, and (3) correlation of the form of the ventricular activation process (QRS) with the anatomy of the ventricles as studied by cross-section.

Twenty-eight normal dogs were studied in the right lateral posture. Bipolar and unipolar limb leads and unipolar circumferential thoracic leads were recorded with a twin-beam electrocardiograph. Frontal, sagittal and horizontal vectorcardiograms were obtained, using the Wilson equilateral tetrahedral reference system. The back point electrode was placed at the dorsal spine of the seventh thoracic vertebra. A special apparatus isolated the QRS loop. The direction of the component vectors was expressed according to Helm's nomenclature.

The direction of inscription of the QRS loop is clockwise in the frontal and sagittal planes, and counterclockwise in the horizontal plane. The length-width ratio is 6:1, 1.6:1, and 4.5:1 respectively. In the frontal and sagittal planes 3 major vectors comprise the loop. Vector 1 is directed cephalically, occurs at 0.006012 sec. after onset of the QRS loop, and has a magnitude of 0.362 mv. directed at $-84°$ in the frontal plane, and 0.459 mv. directed at $-39°$ in the sagittal plane. Vector 2 is directed caudally, occurs at 0.02154 sec., and has a magnitude of 1.015 mv. directed at 74° in the frontal plane, and 0.942 mv. directed at 87° in the sagittal plane. Vector 3 is directed cephalically, occurs at 0.03173 sec., and has a magnitude of 0.229 mv. directed at $-106°$ in the frontal plane, and 0.205 mv. directed at $-129°$ in the sagittal plane.

The horizontal QRS loop has 2 major component vectors. 1. The initial ventral vector occurs at 0.01169 sec. and has a magnitude of 0.676 mv. directed at 79°. 2. The terminal dorsal vector occurs at 0.02789 sec., has a magnitude of 0.253 mv., and is directed at $-82°$.

In all cases there was excellent correlation between actual electrocardiograms and the scalar electrocardiogram derived from the vectorcardiogram. There was also correlation between component parts of the QRS loop and the anatomic location of the areas activated.

Summary. The spatial QRS loop of the normal dog is characterized by 3 major vectors. The first, corresponding to the activation of the interventricular septum, is directed cephalically, ventrally and to the left. The second and largest vector represents activation of the thickest portion of the left ventricular

myocardium, and is directed caudally, slightly dorsally and to the left. The third vector, the smallest, is directed cephalically, dorsally and to the right. The third vector and terminal portion of the second vector represent activation of the left ventricular base.

Clinical Interpretation of Brachial Artery Pressure Tracings

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A study of the direct brachial artery pressure tracing in 250 patients was made to determine the clinical usefulness of the procedure, especially in the evaluation of aortic stenosis. In 56 patients, including 30 with clinical evidence of aortic stenosis, findings at autopsy, operation, or left heart catheterization were available for correlation.

Only 6 of 66 patients with aortic stenosis showed a systolic upstroke shorter than 0.13 sec. in duration. Only 1 completely normal tracing has been encountered in a proven severe case of aortic stenosis, and 17 of 20 such cases have shown upstrokes longer than 0.18 sec. The Valsalva maneuver has been helpful in bringing out the characteristic prolonged upstroke and anacrotic notch.

However, 72 patients without evidence of cardiovascular disease have shown upstroke times ranging widely, up to 0.24 sec., sometimes with an anacrotic notch. An abnormal upstroke time alone, therefore, does not necessarily indicate aortic stenosis, but a wholly normal tracing is rarely found with *significant* aortic stenosis.

Twenty-six patients with myocardial failure, without valvular disease, showed a wide range of upstroke times, similar to the normal group.

None of the changes in the pressure tracing in aortic insufficiency, including wide pulse pressure, low diastolic pressure, bifid peak, or flattened dicrotic wave, were specific, being seen alike in fever, anemia, thyrotoxicosis, and severe atherosclerosis of the aorta. In aortic insufficiency, the direct arterial pressure tracing is useful as a measure of the diastolic pressure, which may not be measured accurately by sphygmomanometer.

It was concluded that, aside from its value in hemodynamic calculations, the brachial artery pressure tracing has value as confirmatory evidence of clinically suspected aortic stenosis, but cannot be diagnostic of that condition, nor indicative of the severity of the lesion.

A Survey of Hemolytic Streptococci from Patients with Rheumatic Fever, Glomerulonephritis, Pharyngitis and the Carrier State

Robert A. Hardin, Robert W. Quinn, and Roy C. Avery, Nashville, Tenn.

Eighty-six strains of β-hemolytic streptococci were isolated from 80 patients. Twenty-five were from patients with acute rheumatic fever, 26 with acute glomerulonephritis, 25 with pharyngitis and 10 from carriers who were not clinically ill. Each strain was grouped and typed and tested for reduction of methylene blue, fermentation of 9 carbohydrates, ability of liquefy gelatin, ability to resist heating at 60 C. for 30 min., and final pH in 1 per cent glucose broth. These results were quite similar for all strains regardless of the type of patient from whom they were recovered. In addition each strain was tested for its ability to produce streptolysin "O," streptolysin "S," streptokinase, hyaluronic acid, hyaluronidase, proteinase and erythrogenic toxin. There were striking differences both qualitatively and quantitatively in the elaboration of these substances by many of the strains and occasionally by strains of the same serologic type. However, no pattern of enzyme production characteristic of any typeable or nontypeable strain or of those strains recovered from patients with any of the 4 clinical syndromes could be demonstrated, nor could there be determined any so-called "rheumatogenic" or "nephritogenic" substances among those studied.

A Comprehensive and Simple Classification of Congenital Heart Disease

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Malformations of the heart and of the great vessels can be divided in 3 groups: (1) Persistent fetal communications; (2) obstructed flows; and (3) obstructed flows with persistent fetal communications.

Persistent Fetal Communications. The characteristic structural feature of this group is that cardiac septation is uncompleted and there is a persistence of fetal communications or passages between the different chambers of the heart and the great vessels. They represent a previous developmental stage in cardiogenesis and are due to a temporary local arrest in growth.

Obstructed Flows. The mechanical disturbance in this group is caused by abnormal narrowing at some points of the cardiovascular tract. These narrowed passages which hinder the normal blood flow do not represent any previous physiologic stage during fetal life and they are due to temporary local accelerated growth.

Obstructed Flows with Persistent Fetal Communications. Combination of the 2 previous structural deviations are the result of periods of temporary accelerated and arrested growth

Enlarged chambers, dilated and "over-riding" vessels are not separate pathologic entities. Their presence is an expression of the degree of interference of the underlying structural deformity with the normal cardiac function. The greater the deviation from the normal anatomic pattern, the earlier and more severe the hemodynamic and clinical repercussions will be.

In the following the characteristic hemodynamic and clinical manifestations of the 3 groups are outlined. A theory is offered on the possible cause and mechanism of the 2 patterns of abnormal growth.

Symptomatic Hyponatremia in Children after Surgery

Herbert S. Harned, Jr., New Haven, Conn., and Robert E. Cooke, Baltimore, Md.

Although hyponatremia has been observed in adults following surgery, particularly after mitral valvulotomy, this has usually been unassociated with symptoms. In children, hyponatremia has been observed as a feature of 2 clinical syndromes, that of water intoxication and that of hyperpotassemia associated with hyponatremia.

Six cases of these 2 syndromes are described, 4 in patients who underwent cardiac surgery. Four of the patients who developed water intoxication with convulsions had excessive water intakes. One patient supplemented normal intravenous fluids with a large oral water intake. An important factor in the development of water intoxication appears to be excessive posterior pituitary hormone production in these patients.

Two cases of hyponatremia with hyperpotassemia presented cardiac decompensation with bradycardia. Both of these patients, who were infants, received the usual fluid and electrolyte therapy postoperatively. Inability to excrete potassium because of the low renal sodium load probably accounted in part for the hyperpotassemia.

The prevention of these disorders by use of preoperative chemistries and proper fluid therapy, the diagnosis by clinical recognition of the syndromes, and the treatment by use of hypertonic and isotonic saline will be outlined.

Prognosis and Classification of Gallop Rhythm

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Gallop rhythm is frequently overlooked. Depending upon the type of diastolic gallop, it is often 1 of the earliest signs of congestive heart failure.

A practical classification of gallop rhythm is presented, which has proved of clinical value as far as diagnosis and prognosis is concerned. Gallops are divided into systolic and diastolic. A systolic gallop heard loudest at the apex is usually a benign finding. The diastolic gallop is further subdivided into 2 types: ventricular or third heart sound type, and atrial. The ventricular type is associated with cardiac decompensation and carries a poorer prognosis. This is not necessarily true of the atrial gallop which may be associated with a prolonged P-R interval or with hypertension in the absence of cardiac failure.

An analysis of several hundred ventricular diastolic gallops studied by the same observer over a period up to 6 years, reveals this to be the pathologic type of gallop. The life expectancy with this type of gallop (approximately 3 to 4 years on the average) is longer than generally thought, but still is a grave prognosis when present. The atrial gallop, in our experience, usually denotes a more optimistic outlook.

Faint ventricular diastolic gallops are the ones most frequently overlooked. If they persist, the prognosis is likewise poor although in general the louder the gallop, the poorer the prognosis. Gallop rhythm is still present and significant even though the ventricular rate is slow (for example, under 100), although it is more difficult to auscult. Technics to "bring out" this pathologic type of diastolic gallop are presented. The relation of gallop rhythm to pulsus alternans and alternation of sounds and murmurs are discussed.

Hemodynamic Consequences of Valve Obstruction: A Physiologic Classification of Mitral Stenosis

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The combination of transthoracic left atrial puncture with right heart catheterization and aortic pulse determinations allows precise information of valve deformities if flow values are known. Four chamber catheterizations with central pulse records were obtained from 34 patients with rheumatic valvular disease involving the mitral and/or aortic valve. No adverse reactions were encountered.

Mean "PC" and left atrial pressures were usually superimposable. In mitral stenosis, the diastolic left atrioventricular gradient ranged from 5 to 25 mm. Hg.

Flow values obtained by 3 independent methods (direct Fick, dye dilutions, or pressure pulse) together with exact pressure analyses allow a prediction of the mitral orifice area with great accuracy because the assumptions previously necessary for such calculation can be replaced by measurable values. The mere presence of a measurable diastolic gradient across the mitral valve is evidence of significant stenosis since the absolute gradient is extremely sensitive to small changes in flow. In addition, the data indicate and re-emphasize an essentially constant rate of diastolic ventricular filling, the importance of diastolic filling time, and the relative ineffectiveness of atrial contraction in mitral stenosis. Minor degrees of mitral incompetence may not be obvious by this technic, but the use of double puncture of the left atrium allows injection of an indicator into the left ventricle and its appearance in blood sampled from the left atrium indicates the degree of regurgitation.

Various divergent physiologic patterns arise. Flow, valve area, and pulmonary arteriolar resistance may vary with considerable independence. High mitral

valve gradients may exist with normal flow and pulmonary artery pressure, with diminished output and normal pressures, or with diminished flow and elevated pressures. The aortic valve obstruction can be treated similarly using the left ventricular aortic gradient and the flow values.

Effect of Carotid Sinus Stimulation on the Electrocardiograms of Normal Individuals

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Forty clinically normal adult males (average age 38 years) were studied for electrocardiographic changes and clinical symptoms induced by carotid sinus stimulation. Stimulation of the carotid sinus was performed in the sitting position, first on the right and then the left side and for a timed interval of 30 sec. Multiple sites of stimulation were used if insignificant results were obtained upon initial massage. The findings included a wide variety of electrocardiographic changes and induced symptoms.

Ten patients (25 per cent) had definitive symptoms, including syncope, nausea and light-headedness. The electrocardiographic effects included ventricular asystole varying from 2 to 5.7 sec. in duration in 9 normal males. Asystole was the result of sinoatrial arrest 4 times on the right and once on the left. Atrioventricular block caused asystole twice on both right and left-sided stimulation. An atrial conduction defect (decrease in amplitude, disappearance, or deformity of the P wave) was produced 18 times on the right and 12 times on left-sided stimulation Direct ventricular muscle effects were absent in these patients; however, significant electrocardiographic changes occurred in all but 3 of these 40 normal individuals. No correlation between symptoms induced and type or degree of electrocardiographic changes produced was obtained. The right carotid sinus was the dominant 1 in symptom-induction and in the production of electrocardiographic changes. However, the left carotid sinus is not to be ignored, as it produced the major changes in 9 of the 37 patients who had significant electrocardiographic effects.

This study serves to underline the importance of the carotid sinus as a reflex center, and to emphasize the clinical impression that the diagnosis of a hypersensitive carotid sinus syndrome cannot be made upon electrocardiographic changes, but only on an *exact* reproduction of symptoms.

Estimation of Cardiac Output, Mean Circulation Time, and Central Blood Volume by Means of Multiple, Graded Dose, Sodium Dihydrocholate Circulation Times

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Sodium dihydrocholate (Decholin), as used for many years to measure arm to tongue circulation time, has proved to be a simple and useful tool in assessing the status of the cardiovascular system. It was felt that Decholin circulation times might provide additional worthwhile information when analyzed from the standpoint of the indicator-dilution principle. For this purpose 3 consecutive rapid injections of Decholin (300 mg., 600 mg., 1200 mg.) were made into an antecubital vein of each of 12 patients with and without cardiovascular disease. The time of onset and complete disappearance of the bitter taste was noted. Simultaneously with 1 of the Decholin injections an indicator-dilution curve, using radiopotassium (K^{42}), was recorded as a reference standard. In each case onset and disappearance time of bitter taste occurred at approximately the same level of concentration on the K^{42} curve. These levels were calculated to correspond to Decholin blood concentrations ranging from 170 to 205 mg./L. The mean concentration for all 12 patients was 180 mg./L. A technic was evolved to construct a Decholin dilution curve using the mean threshold concentration for Decholin taste and onset and disappearance times from the 3 graded doses in each patient. From these curves slope, cardiac output, mean circulation time, and central blood volume were estimated and compared with the same parameters calculated from the K^{42} curves. The maximum deviation from values obtained from the K^{42} curves was for slope 26 per cent, cardiac output 29 per cent, mean circulation time 21 per cent, and for central blood volume 28 per cent. For the 12 patients studied the mean ratios (Decholin/K^{42}) for slope, cardiac output, mean circulation time, and central blood volume were 1.03, 0.93, 1.00, and 0.94 respectively. It is believed that Decholin circulation times made at the bedside can provide more information pertinent to cardiovascular hemodynamics than has heretofore been obtained.

Paroxysmal Supraventricular Tachycardia Complicating Organic Heart Disease

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Paroxysmal supraventricular tachycardia has been generally considered a benign, well-tolerated arrhythmia usually occurring in normal hearts. The true incidence of the disorder in normal hearts is difficult to determine because it is often transient and not observed clinically.

In reviewing the clinical records of 175 consecutive patients who showed electrocardiographic findings of this disorder, we have found that a majority of our patients (approximately ¾) had organic heart disease. Of this group ⅔ were of arteriosclerotic, and ½ were of hypertensive etiology. Less common etiologies included heart disease of luetic, rheumatic, pulmonary, or congenital origin. Frequently 2 or more etiologic factors were present in the same pa-

tient. In about 10 per cent of cases of organic heart disease the disorder complicated recent myocardial infarction, with a most serious prognosis and low survival rate. Most of the cases of the arrhythmia with partial A-V block followed digitalis intoxication in patients with serious organic heart disease.

Whenever paroxysmal supraventricular tachycardia complicated organic heart disease, the disorder was usually poorly tolerated, frequently resulting in congestive failure, coronary insufficiency or shock. If allowed to persist in such cases, the disorder often resulted in death. It was also poorly tolerated in the 11 infants or children in which it occurred (some with normal hearts), where the excessively rapid heart rates produced congestive failure.

The termination of the disorder in organic heart disease patients was usually much more difficult than in patients with normal hearts. Results of our experiences indicate that rapid digitalization may be life-saving if digitalis is not a causative factor. In the A-V block cases complicating digitalis therapy, cessation of digitalis and administration of potassium salts proved most effective.

Myocardial Transfer of Potassium, Sodium and Calcium in Heart Failure after Acetylstrophanthidin

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Previous studies in this laboratory in the intact normal dog have demonstrated that the fast acting digitalis analogue, acetylstrophanthidin, given rapidly intravenously in therapeutic doses causes an abrupt myocardial loss of potassium and a greater myocardial uptake of sodium with concomitant decrease in left ventricular stroke work. To determine if similar changes occur in congestive heart failure, 7 untreated patients in low output failure studied by coronary sinus catheterization were given 1.1 mg. of acetyl strophanthidin with determinations of the myocardial arteriovenous difference of Ca, Na, K, O_2, CO_2, glucose, lactate, pyruvate, pH and hematocrit in the control period and at frequent intervals after drug administration.

Control observations showed no significant myocardial A-V difference of electrolytes. In contrast to the normal dog, after strophanthidin there was in the patients an increase in left ventricular stroke work from 61 to 82 Gm. M., and no significant myocardial uptake of sodium. Similar myocardial potassium loss occurred after drug administration in both groups with maximum negative A-V difference of 0.70 ± .42 mEq./L. (K_A 4.40 mEq./L., K_{CS} 5.10 mEq./L.) in the patients. There was neither myocardial uptake nor loss of calcium.

Control myocardial substrate extraction was normal in failure patients, but after strophanthidin there was myocardial release of glucose occurring shortly after K loss. There was no change in A-V difference of lactate, pyruvate, O_2, CO_2, pH or hematocrits after drug administration. Characteristic electrokymograph repolarization changes of digitalis were observed, but arrhythmias did not occur.

The data are consistent with the theses that the positive inotropic effect of digitalis in heart failure may be dependent upon diminished internal ionic content effected by movement of K from the cell, and that the negative inotropic effect observed in normal dogs may be related to an increased internal ionic content of the cell as a result of a greater Na ingress than K loss.

Levophed (Arterenol Bitartrate) Therapy in Acute Myocardial Infarction Including Case Report of Recovery Following Unusually High Concentration

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A case is presented of extensive acute myocardial infarction with secondary shock and congestive heart failure. Levophed therapy was given for 3 weeks and had to be increased to a concentration of 7 ampoules per 1,000 ml. (56 μg. of arterenol bitartrate). This is almost twice the highest concentration reported in the literature. Thus stronger solutions should be used if necessary and may be life-saving. As a result of over 20 cases treated with Levophed, some other views will also be presented as follows:

1. One should not wait for the actual signs of shock, but if the systolic pressure remains under 95 mm. Hg (or under 100 in a known hypertensive) in spite of oxygen and morphine from 1 to 3 hours, Levophed should be started.

2. If actual signs of shock are present, it should be started immediately. If the desired response is not instantaneous, one should keep increasing the concentration without delay.

3. In heart failure one should reduce the drops by increasing the concentration (e.g., 3 ampoules at 20 drops rather than 1 ampoule at 60 drops/min.).

4. All patients should have special nurses and blood pressure should be taken every few minutes at first and thereafter every 15 min. The nurses should be carefully instructed to increase or decrease the concentration as the blood pressure changes.

5. Another need for constant watching is the danger of interstitial escape of Levophed. The best therapy is immediate subcutaneous injection into the involved area, of 10 to 20 ml. distilled water (with 3 to 5 ml. 2 per cent procaine which will stop the pain immediately). Thus diluting the Levophed and preventing necrosis of tissue.

6. After several days of Levophed therapy, one should do a venous cutdown and insert a polyethylene tube. A femoral vein cutdown may be lifesaving when peripheral veins are unobtainable.

Studies in Differential Vectorcardiography of the Dog. II. Early Changes in QRS Vectorcardiogram and Electrocardiogram Following Experimental Left Circumflex Coronary Artery Occlusion

Herman K. Hellerstein and Robert L. Hamlin, Cleveland, Ohio.

In the present study, previously unreported early QRS vectorcardiographic and electrocardiographic changes occurred consistently and uniformly after experimental coronary occlusion, in addition to usual ST and T changes.

Loose ligatures were placed around the left circumflex coronary artery of open-chested Nembutalized dogs; the chests were closed, the lungs reinflated, and the coronary artery was occluded for a period of time from 2 to 20 min. Continuous electrocardiograms (leads I, aVF and back point) were recorded, and isolated QRS loops of frontal, sagittal and horizontal planes were photographed every 15 to 30 sec. The Wilson equilateral tetrahedral reference system was used with the back electrode placed on the dorsal spinous process of the seventh thoracic vertebra.

In each of 13 experiments (6 dogs), the following sequence of events occurred. QRS changes: There was a slight (up to 10 per cent) nonpositonal decrease in amplitude during the first 15 to 20 sec., followed by a progressive increase in duration, and of amplitude until a maximum of 150 to 200 per cent of the control value was reached in 2 min. after occlusion. Changes in the amplitude and duration of the vectorcardiogram occurred approximately 0.014 sec. after onset of the QRS complex, and persisted until the beginning of the ST-T complex. From the period of 0.014 to 0.029 sec. after onset of the QRS, the calculated spatial velocity of the QRS complex and loop was unchanged. The increased magnitude probably represents the unopposed, normal, activation of nonischemic myocardium, (septum, ventral-anterior apex of left ventricle, and right ventricle). Since the velocity of activation decreased from 0.029 sec. to the onset of the ST-T, an increase in magnitude at this time represents tardy, unopposed and slower activation of the ischemic diaphragmatic myocardium.

The effective spatial vectorcardiogram (representing the effects of left circumflex ligation) was derived by vectorially subtracting the control from the resultant instantaneous vectors. Uniformly the long axis of the spatial effective vectorcardiogram is directed caudally, and with slight dorsoventral and left-to-right deviation, similar to the anatomic orientation of the ischemic myocardium.

ST-T changes: Opening of the QRS loop (caudally and slightly dorsally) represents ST-T deviation (elevation in aVF and back point leads) and occurred within 15 sec. after artery ligation reaching a maximal value within 75 sec. Both QRS and ST-T changes were reversible, returning to control values within 2 min. after the ligature was released.

Summary. Experimental acute coronary insufficiency produces early changes in the magnitude and velocity of myocardial activation as demonstrated by QRS changes in the spatial vectorcardiogram and electrocardiogram.

An Accurate Lead System for Vectorcardiography and Spatial Electrocardiography

Robert A. Helm, Cincinnati, Ohio.

The following electrode placements have been devised for recording 3 orthogonal leads which possess relatively uniform vector properties for all portions of the heart: 1. Transverse lead or lead X—a square saline-containing synthetic sponge electrode extending from the left midclavicular line to the left posterior axillary line, and a small conventional limb electrode located midway between the right anterior axillary line and the right midaxillary line. Both electrodes are placed at the level where the fifth intercostal space intersects the parasternal lines. 2. Sagittal lead or lead Z—a square saline-containing synthetic sponge electrode placed at the same transverse level as the sponge electrode of lead X and extending from (but not in contact with) the anterior margin of the latter electrode to a symmetrically identical longitudinal line on the right anterior chest, and a small conventional limb electrode located midway between the vertebral and left scapular lines approximately 1 cm. caudad to the level of the small limb electrode of lead X. 3. Longitudinal lead or lead Y—a limb electrode placed on the forehead or in the submandibular region and a network of 2 limb electrodes, 1 placed at any convenient location on the left leg and 1 placed in the same longitudinal line as the small electrode of lead Z at a transverse level approximating the lower margins of the sponge electrodes of leads X and Z. Based on Frank's data for his 22 dipole location, the magnitude of the vector of each of these leads is taken to be $2\sqrt{2}$ or 2.83 mv./ma.-cm. Theoretic and experimental justification for this lead system, which is well adapted to cathode-ray vectorcardiography, will be cited. In addition, a practical clinical method will be described and illustrated in which the 3 orthogonal leads may be systematically combined to yield a mosaic of 13 scalar leads, the vectors of which lie on 9 well-defined planes.

Early Detection of Retinal Vascular Abnormalities in Diabetes Mellitus

John B. Hickam and Herbert O. Sieker, Durham, N. C.

It is now apparent that patients with diabetes mellitus often develop widespread disease of the small blood vessels, in addition to the well-known vascular complications of atherosclerosis and hyper-

tension. Early detection of this disorder has been difficult. Diabetic small vessel disease is manifested in the retina by capillary aneurysms and venous abnormalities, but these are advanced changes. It is the purpose of this report to describe experience with a method which appears useful for the early detection and quantitation of retinal vascular abnormalities in diabetes.

The method consists of measuring, by fundus photography, the per cent decrease in diameter of the larger retinal vessels which occurs while breathing oxygen for 5 min. In 50 normal subjects, aged 13–76 years, the retinal arteries had a diameter decrease of 11:6 ± 4.7 per cent and the veins 14.9 ± 6.5 per cent. In 50 diabetic patients, aged 16–76 years, there was a statistically significant decrease in arterial contraction or "reactivity" (5.7 ± 4.7 per cent) but not in venous reactivity (10.7 ± 6.7 per cent). The diabetic group was further examined for relationships between loss of retinal arterial reactivity and certain other complications of diabetes. When retinopathy was present, arterial reactivity was greatly reduced (3.9 ± 4.1 per cent in 28 patients). The 22 diabetics with normal fundi showed no significant reactivity loss as a group (8.0 ± 4.8 per cent), but individual members had marked reductions. Twenty-one patients had peripheral or autonomic neuropathy, but the arterial reactivity of this group was not different from those without neuropathy.

The loss of retinal arterial reactivity in diabetes appears to be independent of hypertension and atherosclerosis. Reactivity is diminished in hypertension, but 32 of the diabetic group were normotensive, and their arterial reactivity was significantly below normal (6.3 ± 4.9 per cent). Atherosclerosis affecting coronary or peripheral arteries in normotensive, nondiabetics is not associated with diminished retinal reactivity.

This simple test shows good promise of reflecting small vessel disease in diabetes.

Effects of Penicillin and Streptomycin on Staphylococcal Endocarditis in Dogs with Aortic Insufficiency

Benjamin Highman, Joseph Roshe, and Paul D. Altland, Bethesda, Md.

Dogs with experimental aortic insufficiency which are given 1 ml. of a culture of *Staphylococcus aureus* intravenously die in about a week and show acute endocarditis, with visceral infarcts and widespread hemorrhagic and suppurative lesions (Fed. Proc. **15:** 518, 1956). The present investigation was undertaken to study the effects of various therapeutic regimes on the pathologic picture and course of the disease. Fifteen dogs with aortic insufficiency were given 1 ml. of staphylococcus culture and treated intravenously with a 5:1 weight ratio of sodium penicillin G and streptomycin sulfate. Each injection usually contained 50 mg. or 83,333 units of penicillin/Kg. body weight. A single antibiotic injection prevented infection when given within 8 hours following the bacterial injection, but was less successful when given 24 hours later.

Five dogs received 4 intravenous antibiotic injections and 2 intramuscular injections of probenecid (10 mg./Kg.) daily for 5 days. Arrest of the disease and healed valvular lesions were noted when treatment was begun 24 and 48 hours after the bacterial inoculation. When treatment was delayed 72 hours, the disease was either completely arrested or a recurrence developed several days after stopping treatment. Treatment with smaller or fewer antibiotic doses prolonged life, but failed to prevent recurrence. Treatment of such recurrence either arrested or modified the infection.

Several dogs were observed for periods up to 3 months. Treatment was intermittent and was stopped entirely if blood cultures became persistently negative. At autopsy, all showed evidence of congestive heart failure secondary to chronic valvular deformities involving the mitral and aortic cusps. One such dog died with acute pulmonary edema several weeks after stopping treatment; postmortem examination revealed marked aortic incompetence due to spontaneous rupture of the right aortic cusp.

These findings re-emphasized the importance of early and adequate therapy in endocarditis.

A Study of the Pressure-Volume Relationship of the Left Ventricle of the Dog

J. P. Holt, Jean Allensworth, John Diana, David M. Collins, and Helga Kines, Louisville, Ky.

In the anesthetized closed chest dog the end diastolic volume (EDV), end systolic volume (ESV), and stroke volume of the left ventricle were determined by means of an electric conductivity method described earlier by 1 of us (J.P.H.), and simultaneously the left intraventricular pressure and intrathoracic pressure were determined. In an attempt to obtain wide variations of pressure and volume of the ventricle the animals were subjected to hemorrhage, plethora, and the breathing of air under negative pressure. Hemorrhage caused a marked reduction in EDV, and plethora caused a marked increase in EDV, while the breathing of air under negative pressure caused little or no change in either EDV or in the "effective" intraventricular pressure. As the EDV increases the ESV, stroke volume, and stroke work increase. Beginning with the smallest posthemorrhagic EDV consistent with life, as the EDV increases severalfold (with an increase in blood volume) there is either no change or a very slight increase in "effective" end diastolic pressure, while after a certain large EDV is reached a small increase in EDV is associated with a large increase in "effective" end diastolic pressure. Beginning with a small "effective" end diastolic pressure and stroke work in the hemorrhaged animal, as the stroke work increases (with an increase in blood

volume), the "effective" end diastolic pressure increases only slightly; after a certain large stroke work is reached there is little or no further increase in stroke work while the "effective" end diastolic pressure increases markedly.

Quantitative Ballistocardiography in Aortic Insufficiency

Carl R. Honig and Stephen M. Tenney, Rochester, N. Y.

An "aperiodic" ballistocardiograph was used to quantitate the hyperkinesis of 14 unselected cases of aortic insufficiency, including 5 with combined lesions. Force varied directly with the severity of aortic regurgitation unless congestive failure or aortic aneurysm coexisted, and in severe insufficiency exceeded 67×10^5 dynes, or 550 per cent of maximum normal. The ballistocardiograph may therefore meet the growing surgical requirement for quantitative evaluation of aortic valve function.

Serial force determinations proved particularly useful for assessing the effects of a Hufnagel valve. Postoperatively, diastolic hypertension and cutaneous vasoconstriction appeared in the distribution of the distal arterial segment, together with throbbing headache and marked increase in force. Over the following 12 months however, force, heart size, and murmur intensity gradually decreased and symptoms of cardiac insufficiency disappeared. The hemodynamic factors responsible for these changes will be discussed, with special reference to the role of vasomotor tone.

The magnitude of kinetic work in aortic insufficiency was estimated ballistocardiographically by determining the increase of force and displacement relative to normal. The product of the relative increases has the dimensions of work, and in the above patient was 90 times normal. Assuming kinetic work to be increased in proportion to its reflection in body motion, and to range normally between 0.05 and 0.25 Kg. M./min., kinetic work in this patient was between 4.5 and 22.5 Kg. M./min. In severe insufficiency kinetic work alone may therefore equal or considerably exceed the total work of a resting normal heart.

Since the arterial "resonating chamber" is open centrally in aortic insufficiency, mass motions of blood associated with the standing wave are minimized. Such patients exhibit small diastolic ballistic vibrations, indicating the importance of the normal resonating arterial column to the genesis of these waves.

Studies on Water and Electrolyte Excretion in Essential Hypertension

Sibley W. Hoobler, John M. Weller, and Paul T. Cottier, Ann Arbor, Mich.

It has been shown that hypertensive subjects excrete more water, sodium, chloride and potassium following an intravenous load of sodium chloride (2.5 per cent) than do individuals with a normal blood pressure. There was no change in the renal hemodynamics (renal plasma flow, glomerular filtration rate and filtration fraction) under load. As long as the renal hemodynamics were within normal range the mean arterial blood pressure paralleled the sodium clearance. In the group of severely hypertensive patients (mean blood pressure 201/131) the sodium clearance decreased with the progressive impairment of the renal function. The sodium clearance appeared to correlate best with the total renal resistance.

Using a simplified salt loading test with fractional urine collections over a 24-hour period, the following observations were made: 1. The resting salt excretion of the hypertensive group was the same as that of the normotensive group during the periods preceding and following the 2 load periods of 1½ hours each. 2. Prior diet did not affect the excretory pattern of sodium, water and potassium following load in any consistent manner. 3. In 4 patients studied so far who had a history of mild labile hypertension, but who were normotensive at the time of the test (their sodium excretion under load) tended to be at the upper limit of the normal range.

These findings suggest that a hemodynamic factor as opposed to a possible metabolic abnormality is responsible for the excess excretion of water and electrolytes in essential hypertension.

A Study of the Influence upon the Spatial Vectorcardiogram of Localized Destruction of the Myocardium of Dog

Leo G. Horan, George E. Burch, and James A. Cronvich, New Orleans, La.

The purpose of these experiments was to study the influence of known localized myocardial destruction upon the configuration of the spatial vectorcardiogram (sVCG) and to evaluate the diagnostic accuracy of the sVCG in the detection and localization of the myocardial loss. Acute localized or diffuse destruction of the myocardium was produced in 22 dogs by burning with soldering iron, acetylene torch, electrocautery or by instillation of formaldehyde in the pericardial sac. Branches of the left coronary artery were ligated in 4 other dogs. The electrocardiogram (ECG) and sVCG were recorded at frequent intervals up to 3 hours after injury.

Except for 2 ligation experiments, the early portions of the QRS sÊ-loop and QRS complex were relatively unaffected. There was, however, a reduction in magnitude of the approximately midtemporal mean instantaneous vectors of the QRS sÊ-loop and corresponding alterations in the QRS complex. Such resulting deformities resembled those previously described for infarction in man. Burns of the right ventricle or pulmonary conus produced little change. The formaldehyde, which uniformly injured the myocardium to about a 3 mm. depth (outer third of

the left and most of the right ventricular wall), produced a pronounced reduction in magnitude and alteration in configuration of the QRS sÊ-loop. The accompanying ECG resembled a monophasic action current.

The directions of displacement of the T sÊ-loop and junction J, (ST segment shift) were predictable from classical electrocardiographic knowledge. Anterior myocardial burns resulted in a dorsally directed T sÊ-loop; diaphragmatic surface burns, in cephalic displacement of the T sÊ-loop; formaldehyde, in orientation of the T sÊ-loop toward the right shoulder; and all injuries, in opposite displacement of J.

This method appears to be a useful tool for correlating the anatomic site of myocardial injury with the recorded electrophysiologic activity of the heart of the experimental animal.

Effect of Reduced Cardiac Output on Tissue Energy Metabolism

William E. Huckabee, Boston, Mass.*

Studies of the rate of tissue anaerobic metabolism of patients with congestive heart failure have shown that this type of metabolism substitutes to a large extent for the inadequate O_2 delivery by the circulation during all grades of exertion in such patients. The effect of simply reducing cardiac output, without causing the other changes typical of chronic heart failure, and the nature of tissue metabolic responses to circulatory changes at complete rest were unknown. The following experiments were designed to clarify these points.

Fifteen dogs were subjected to mild pressure-breathing with air so as to reduce cardiac output by 15 to 50 per cent. The A-Vo_2 increased commensurately, and arterial blood O_2 remained unchanged or increased by variable amounts. Because of these contrary changes it was not possible to know from such data whether O_2 deficiency was present in the tissues during any experiment. Net rates of anaerobic metabolism of body tissues as a whole were estimated as previously described from differential rates of change of total body pyruvate and lactate.

Results. A. Nine (66 per cent) of the animals exhibited progressive accumulations of "excess lactate" from anaerobic metabolism at rest. B. Six (33 per cent) showed no change or a decrease in excess lactate; the latter unusual process was found characteristic of 100 per cent O_2 breathing (1 atmosphere) in 4 experiments. Increases and decreases in mixed venous blood O_2 were noted in both groups A and B and the decrease of cardiac output was about the same in both; rising and falling blood lactates were found in both groups and showed no relation to changes in blood O_2 or excess lactate.

It was concluded that simple reductions of cardiac output may or may not result in deficiency of O_2 supply to tissues relative to their metabolic energy requirements at rest, but in either case blood O_2 measurements and rates of blood flow do not give an adequate indication of its presence.

Psychiatric Evaluation of Patients Undergoing Cardiac Work Evaluation

Albert M. Hurley and Donal R. Sparkman, Seattle, Wash.

The Washington State Cardiac Work Evaluation Clinic is concerned with the examination of patients who have employment problems presumably due to heart disease. These patients are referred by practicing physicians in the State of Washington. Many of these patients were noted to have significant emotional problems which interfered with their return to work. For this reason it was decided to have a routine psychiatric examination of each patient referred to the Clinic.

This is a report of the result of the psychiatric examinations for a period of approximately 2 years and covers the findings of a group of 200 patients. Interviews were limited to a single 1 hour period.

One hundred twenty-six of the total of 200 patients were found to have significant psychiatric problems which were interfering with their optimum functioning. Of these 126 patients 71 were neurotic, 15 were psychotic, 36 had character disorders, 2 were mentally defective and 2 were alcoholics. Sixty-eight per cent (47) of 70 patients with coronary artery disease had significant emotional problems and 42 per cent (14) of 34 patients with rheumatic heart disease had significant problems. Ninety-four per cent (15) of 17 patients with no heart disease referred to the Clinic had significant emotional problems. Eight patients with heart disease were seriously disturbed by emotional problems but still able to work.

The results of the psychiatric studies confirm the impression that a large number of cardiac patients being considered for return to work had significant emotional problems which were as important a part of their total disability as was their heart disease. Awareness of these emotional maladjustments permitted a more intelligent evaluation and disposition of these patients. An appreciation of this fact should be useful in the rehabilitation of patients with cardiac disease.

Pre and Postoperative Clinical, Electrocardiographic and Hemodynamic Data of Thirty Patients Having Undergone Circumferential Suture of the Mitral Ring for the Correction of Mitral Insufficiency

O. Henry Janton and Gerardo Voci, Philadelphia, Pa.

From January 1955 to June 1956, 30 patients were operated upon for the correction of severe mitral insufficiency. The technic employed for the correc-

tion of the insufficiency was circumferential suture of the mitral valve ring.

The purpose of this communication is to present the clinical and laboratory data both pre and postoperatively in these patients.

The pertinent findings to be presented are: (1) the marked chronic congestive heart failure occurring in the majority of these patients, many of whom were considered to be intractable to medical therapy, (2) the presence of atrial fibrillation associated with electrocardiographic evidence of right, left or combined ventricular hypertrophy, (3) radiologic evidence of marked enlargement of the heart chambers, and (4) altered dynamics in the lesser circulation before, during and after operation.

Hemodynamic data indicate that mitral insufficiency can be successfully corrected. The altered dynamics were dependent upon the status of the myocardium and particularly the pathologic nature of the mitral valve. The more dramatic hemodynamic changes were usually associated with the lesser degrees of valvular pathology found at surgery.

Seventeen of the 30 patients died. Eight died on the operating table, 3 died within a few days after surgery, and 6 died from 2–8 months after surgery.

To date the 13 surviving patients have shown minimal to moderate functional improvement. The postoperative roentgenograms show an appreciable reduction in cardiac size. The electrocardiograms several months after surgery show no significant axis deviation or improvement in the previous signs of ventricular hypertrophy.

Electrocardiographic Changes Following Circumferential Suture of the Mitral Ring for the Correction of Mitral Insufficiency

O. Henry Janton, Gerardo Voci, and Robert P. Glover, Philadelphia, Pa.

Several interesting electrocardiographic changes were observed in 19 cases following circumferential suture of the mitral ring for the correction of mitral insufficiency. These changes were: 1. A complete A-V block appeared in all cases at the time the circumferential suture was tied. This conduction disturbance lasted but a few seconds in the majority of the patients and for several days in 2 instances.

2. Patterns of pericardial reaction were present constantly for several days in every case.

3. Within 1 to 2 weeks after surgery, superimposed patterns of anterolateral myocardial ischemia were observed in 10 cases. In 2 of these cases the altered T wave became progressively normal within 3 months after surgery.

4. Incomplete right bundle-branch block occurred in 1 case and incomplete left bundle-branch block in another.

The possible reasons for these postoperative electrocardiographic changes will be considered.

Infrequency of Myocardial Infarction in Patients with Thyrotoxicosis

William A. Jeffers, Philadelphia, Pa., Edward Rose, Philadelphia, Pa., and Donald S. Littman, Little Silver, N. J.

The purpose of this report is to point out the rarity with which cardiac infarction has been observed to occur in the presence of active thyrotoxicosis. A careful perusal of the literature substantiates this point of view. From our review we have been able to find only 1 case report indicating that cardiac infarction occurred in a thyrotoxic individual.

During the past 4 years we have observed this rare coincidence in 3 additional patients. The course of their cardiac infarctions has been somewhat atypical. The case histories of these patients are summarized, and their electrocardiographic findings are presented.

Unfortunately, studies of lipid metabolism were not performed before and after thyrotoxicosis was brought under control in our 3 patients. Others have described marked differences between the patterns in thyrotoxicosis and hypothyroidism. The rarity of this clinical coincidence has led us to embark upon such studies in patients with thyrotoxicosis. Our findings will be reported elsewhere. A further explanation for the rare coincidence of these 2 disorders is to be found in the work recently reported by Rowe and associates. They found that the hypermetabolic state of thyrotoxicosis includes the myocardium. When patients were restored to the euthyroid state with treatment, the cardiac output, cardiac work, coronary blood flow and myocardial oxygen consumption became normal, and the coronary vascular resistance increased.

With the advent of more effective medical measures for suppressing thyroid toxicity, it is conceivable that patients with coronary atherosclerosis and thyrotoxicosis may be relieved of their attacks of angina more readily, but may suffer cardiac infarction when thyroid toxicity is brought under control unless steps are taken to avoid elevation of serum lipid levels.

Range of Blood Pressures in the Framingham Study

Abraham Kagan, Framingham, Mass., Felix E. Moore, Bethesda, Md., and Thomas R. Dawber, Framingham, Mass.

An analysis was made of the distribution of blood pressure measurements in the initial examination of the population sample of the Framingham Study. The sample comprised 4,494 randomly selected persons between the ages of 30 and 60. The subjects had a comprehensive and standardized medical examination. The causal blood pressures obtained were correlated with other observed variables in-

cluding clinical, electrocardiogram, and x-ray evidence of heart disease.

The mean blood pressures, considered by age and sex, were found to be higher than those reported in previous studies. In both sexes, the blood pressure increased with age. This rise was much greater in the females than it was in the males. The mean systolic and diastolic pressures were lower in females than in males up to the age of 40; over the age of 50, these pressures were higher in the women than in the men.

A study was made of the relationship between blood pressure levels and cardiac enlargement in a smaller group, derived by the elimination from the larger sample of the 293 subjects with coronary heart disease, rheumatic heart disease and other nonhypertensive heart disease. In each age group of the remaining 4,201 subjects, the mean blood pressures of those with cardiac enlargement was higher than the mean blood pressures of those without enlargement. A further elimination of all those subjects with cardiac enlargement, electrocardiogram abnormalities, or evidence of a cerebrovascular accident, left a remaining group of 3,226 subjects without objective evidence of cardiovascular disease. An analysis of the blood pressures in this group revealed only a slight upward trend with age among males, but a persistent and marked upward trend with age among females.

The distributions of blood pressures closely approximated the normal curve. There was no evidence in the distributions, or in the correlations with x-ray and electrocardiogram abnormalities, to suggest a sharp line of demarcation between normal and abnormal blood pressure.

Observations of Postoperative Myocardial Infarction

Daniel Kahn, Woodrow W. Lindenmuth, and Massimo Calabresi, West Haven, Conn.

Nine cases of postoperative myocardial infarction have been observed among 897 consecutive surgical procedures, 451 of which were major operations. Five other patients had persistent electrocardiographic abnormalities, although a conclusive diagnosis of infarction could not be reached.

The high incidence of this complication in our material as compared with the reported statistics is noted. As postoperative follow-up procedures are not standardized, simply comparing figures is meaningless. Although we cannot exclude that the high incidence in our material is in part fortuitous, it is pointed out that a high index of suspicion and the close cooperation between medical and surgical services have led to a comprehensive postoperative medical study in most of our patients. The age of the 9 patients ranges between 38 and 74. The types of operation vary from an endoscopic procedure to subtotal gastrectomy. Types of anesthesia, duration of the operations, and observations during surgery will be reported. The clinical course is frequently atypical and the diagnosis—suspected clinically—is based on electrocardiographic findings. Three cases have died, 2 of them due to the infarction; the autopsies have confirmed the clinical diagnoses.

Uncertainty and pitfalls in preoperative prognosis are apparent from our experience with repeated operations in this series and from observations in emergency surgery in "cardiac poor risk" cases without postoperative complications.

Management of these cases, especially in relation to early mobilization, to use of anticoagulants and to thrombotic tendency in the postoperative period must be individualized.

Because of this experience, all our surgical patients age 45 and over have now preoperative and postoperative electrocardiographic studies; all "suspicious" cases, regardless of age, are followed by the cardiac service. Preliminary results of this study and of an analysis of 6 years experience with preoperative electrocardiographs in patients 45 years of age and over will be briefly discussed.

Reaction of Sera from Patients with Acute Rheumatic Fever with Connective-Tissue and Vascular Constituents of Biopsied Rheumatic Heart Tissue

Melvin H. Kaplan,† Boston, Mass.

The fluorescent antibody technic as described by Coons and Kaplan (J. Exper. Med. **91:** 1, 1950) has been modified and adapted to the study of autoimmune bodies reactive with tissue components (see Kaplan, Fed. Proc. **15:** 338, 1956). This technic was employed in the present study. It involved the use of fluorescent antihuman gamma globulin as an immunohistochemical stain to demonstrate a specific reaction between a gamma globulin in the sera of patients with acute rheumatic fever and unfixed frozen tissue sections taken from biopsied rheumatic auricular appendages. In this study 26 specimens from biopsied rheumatic hearts and 6 specimens from nonrheumatic hearts obtained at postmortem were tested for possible reactivity against sera from more than 100 individuals. Included were sera from 70 patients in various phases of acute rheumatic fever, 20 convalescent patients, considered inactive, and 30 nonrheumatic individuals, including healthy and ill persons.

The results of this study showed that of the 26 rheumatic hearts examined, 11 were reactive with a number of sera drawn from patients with active rheumatic fever. Reactive sera were obtained from 13 of the 70 patients with rheumatic fever. The sera of all 20 patients who were convalescent and considered inactive showed no reactivity. Of the 30 nonrheumatic individuals tested thus far, including 8 with scarlet fever, 1 patient has been positive with a presumptive diagnosis of osteomyelitis. None of the rheumatic sera were reactive with the nonrheumatic

hearts. In addition, 9 of the rheumatic hearts showed the presence of bound gamma globulin, whereas in none of the normal hearts could bound gamma globulin be demonstrated. In the case of 15 of the rheumatic hearts, neither reactivity with positive sera nor the presence of bound gamma globulin could be demonstrated.

The sites of bound gamma globulin and the sites of interaction between rheumatic sera and rheumatic heart tissue were identical: (1) endothelium and walls of capillaries and small arteries, (2) sarcolemma and connective tissue septae, and (3) to a significantly lesser extent, myocardial cell sarcoplasm.

Although the reactive gamma globulin in the serum of rheumatic patients has as yet not been specifically characterized as an antibody, these studies are consistent with the concept of an autoimmune phase in the pathogenesis of rheumatic carditis.

Present Status of the Pregnant Cardiac Patient

Jack M. Kaufman and Paul Ruble, Detroit, Mich.

A brief summary of our experience in the handling of the pregnant cardiac patient is presented. We have reviewed the cases from the major institutions of Detroit. Emphasis is placed upon cardiac surgical procedures during pregnancy. Twelve commissurotomies were done during pregnancies. No maternal mortality was encountered. Eleven live babies were delivered. Three patients were operated for patent ductus ligation during pregnancy. These patients were in cardiac failure at time of surgery. All 3 had uneventful deliveries. Ten other patients with patent ductus arteriosus had uneventful deliveries.

Danger of reversal of shunt following delivery may be easily combated by slow drip of norepinephrine. One case of tetrology of Fallot subjected to 2 Blalock procedures delivered, quite readily, a normal baby. Our conclusions are: 1. That cyanotic heart disease per se is only a relative obstacle to successful pregnancy. 2. That mitral commissurotomy may be performed quite readily during pregnancy with very low mortality. 3. That therapeutic abortion for cardiac reasons is very rarely indicated. 4. That ligation of patent ductus during pregnancy is a relatively easy procedure. 5. That reversal of shunt at delivery may be obviated by slow intravenous drip of norepinephrine at delivery. The general cardiac management of the pregnant cardiac patient is considered.

Clotting Studies with Human Blood at 28 C.

Kurt N. von Kaulla, Denver, Colo.*

Comparative clotting studies of hypothermic patients during anesthesia and operation consistently revealed, among other findings, a more complete prothrombin consumption in recalcified plasma when clotted and incubated at 28 C. than at 37 C. The sera were obtained 90 min. after complete clotting, and 30 min. after removal of fibrin. It was then demonstrated that this effect could be produced with any normal whole blood or citrated plasma, provided the specimen was drawn without any contamination by tissue thromboplastin. Siliconized equipment reduced the effect but did not eliminate it. Thrombin titration during clotting, at both temperatures, showed the presence of more thrombin in the cooler specimens at times when thrombin formation reached its peak. This peak was often, but not always, attained earlier in the 28 C. than in the 37 C. specimens. No increased activity of factor V or VII was found in the serum of 28 C. specimens.

If 28 C. sera are added in 50 per cent concentration to high speed centrifuged platelet-poor plasma, the deficient prothrombin consumption is normalized. Sera of 37 C. specimens do not show this effect. A similar activity in 28 C. sera can be detected in contrast to 37 C. sera with stored frozen and rethawed hemophilic A plasma. These sera added in 25 per cent concentration or more to hemophilic plasma, shift prothrombin consumption, intensity, and speed of fibrin formation toward normal values. The described activity found in 28 C. specimens at various degrees, is assumed to be due to thromboplastin abnormality slowly inactivated by inhibitors not entirely active at lower temperatures. Its abnormal activity may possibly deviate subsequent clotting and hemostasis in hypothermic patients.

Potent Fibrinolysis in Man by Intravenous Pyrogens

Kurt N. von Kaulla, Denver, Colo.*

Purified protein-free pyrogens from *S. abortus equi* (I), and *E. coli* (as acetylated derivative) (II), were received intravenously by 49 individuals. In accordance with Eichenberger's observation, marked fibrinolysis was induced, effective doses in our experiments being 0.2 μg. for I, and 100–300 μg. for II. In contrast to streptokinase, this material is ineffective in vitro and in animals. Fibrinolysis is detectable 60 min. after injection, has peak activity at 105–120 min. and disappears, depending upon dosage, in 150 to 240 min. Side reactions (chills, headache, dizziness), when present, are most intensive before or at fibrinolysis peak and disappear before temperature maximum at 167 to 220 min. Effective antipyresis does not interfere with lysis. Marked fibrinolysis, i.e., clot dissolution time less than 3 hours, was induced in 27 patients, 13 having temperatures below 38 C., and 5 below 37.5 C. Some patients had fever without lysis. II induces potent lysis with less fever than I, 300 μg. producing lysis times between 25 and 180 min. Antifibrinolysin is then frequently, but not always, reduced. Fibrinolytic plasma (5 per cent) induces lysis in preinjection

specimens. The euglobulin fractions of active samples may undergo fibrinogenolysis on incubation. They require more time for spontaneous fibrinolysis after subsidence of the fibrinolytic effect than before injection. Recordings reveal that lysis starts slowly, often before completion of fibrin formation, then proceeds with constantly increasing speed, and slows down when most fibrin is dissolved. Following injection, the time from recalcification to onset of fibrin formation becomes progressively shorter, and fibrin formation rate speeds up with maximum at 150 min. After repeated injections, the fibrinolytic response is lessened. Marked fibrinolysis did not enhance present bleeding tendency nor increase blood content of lochia in 21 postpartum patients (second to fourth day). Therapeutic pilot tests were encouraging.

Recognition and Quantitation of Valvular Insufficiency from Indicator-Dilution Curves

John R. Keys, Edward Woodward, Jr., H. J. C. Swan, Howard B. Burchell, and Earl H. Wood, Rochester, Minn.

Dilution curves were recorded continuously and simultaneously from the radial artery and left atrium after injection of T-1824 into the left ventricle, left atrium, pulmonary artery and superior vena cava in 12 patients with acquired heart disease studied by combined catheterization of the right and left heart and aorta.

Characteristics of curves obtained in valvular insufficiency suggest a means of recognition and quantitation of regurgitation. These characteristics are disproportionate prolongation of the disappearance slope, low peak concentration, and absence of a recirculation peak.

These deviations from normal time and concentration relationships of dilution curves may be used as an index of valvular insufficiency if intracardiac shunts are excluded. For example, the ratio of dye-disappearance time after peak concentration to the time required to build up to a peak concentration is normally less than 1.6 (average = 1.3; range = 1.2–1.6). Delay in disappearance of dye due to insufficiency may increase this ratio to 2.0 or more. Similarly, since the peak concentration produced by injection of a given dose of dye into the pulmonary artery is known (average = 89 and range = 70–118 mg./L./mg. of injected dye/Kg. body weight), a decrease in this value to less than 70, as may occur in mitral insufficiency, serves as an index of this condition.

Effective forward flow may be determined from the dilution curve by the Hamilton method; a value affected by both forward and regurgitant flow is obtained from the forward part of a dilution curve. The difference between these 2 values is related to regurgitant flow. This method has the advantage of simplicity over the variance method of Korner and Shillingford to assess the severity of valvular regurgitation.

Phenomenon of Electric Alternans in Single Ventricular Fibers of the Frog Heart

Morris Kleinfeld, Edward Stein, and John Magin, New York, N. Y.

Electric alternation was recorded from single ventricular fibers of the frog heart in 14 experiments employing l-thyroxine, triiodothyronine and acute anoxia. In approximately 88 per cent, electric alternation was present simultaneously in the indirect bipolar electrocardiogram and the ventricular fiber of the intact heart. In the remainder, electric alternans was present only in the indirect bipolar electrocardiogram. In 2 experiments employing an isolated ventricular strip, electric and mechanical alternans were observed simultaneously after adding triiodothyronine to the Ringer's solution and after acute anoxia. The phenomenon was transitory, unrelated to heart rate and more frequently associated with decreased cardiac contractility.

Four types of electric alternation of the membrane action potential were observed. These were alternation in (1) rate of depolarization, (2) rate of repolarization, (3) magnitude of the membrane action potential, and (4) hyperpolarization. Usually the alternation involved several phases of the action potential.

The present data does not permit the presentation of a unified hypothesis to explain the mechanism underlying the various forms of electric alternation described. It is attractive to speculate that changes in magnitude, rate of depolarization, rate of repolarization and degree of hyperpolarization of the action potential are on the basis of periodic variations in permeability of the membrane to Na and K ions. With regard to Na^+, the changes in magnitude and rate of depolarization of the action potential may be due either to variations in the availability of the carrier substance per se or to variations in the combination of sodium and carrier substance.

The exact mechanism by which l-thyroxine and triiodothyronine alter the membrane permeability to these ions is unexplained.

An Attempt to Demonstrate Pulmonary Arteriovenous Anastomoses in Rabbits, Cats and Dogs, and Discussion of Literature Pertaining to such Shunts

William H. Knisely, W. M. Satterwhite, Jr., and John M. Wallace, Durham, N. C.*

The possibility of arteriovenous anastomoses in normal lungs is relevant to understanding transpulmonary passage of metastases, and circulatory and respiratory dynamics.

Because Prinzmetal's 1948 experiments were fre-

q ently quoted as "proof" of such anastomoses, we r peated them. He injected glass beads via ear or j gular vein, right ventricle or pulmonary artery in 6 rabbits, 3 dogs and a cat, recovered beads from 9 li ers and 1 pulmonary vein, and concluded anast moses were demonstrated.

We attempted to demonstrate anastomoses in 120 r bbits, 25 cats and 15 dogs by injecting spores, g ass beads or seeds from 10 to 2,500 microns in d ameter. We varied the site and rates of injections, v nous and/or arterial pressures and animals' p sture during injections, opening of thorax and/or a domen, and the use of pentobarbital, heparin and s liconed beads. Particles were looked for in transi luminated living organs, blood from right heart, p lmonary veins, left heart, aorta, abdominal inf rior vena cava (IVC) and from hydrolyzed spleen, liver, kidneys and muscle.

Liver and kidneys frequently contained many beads although few were found elsewhere. In 7 animals to determine if beads could have retrogradely entered the liver, the thoracic IVC was divided, each end cannulated, and the blood transferred caudal to cranial with syringes. Beads could only enter the liver by hepatic artery and portal vein. None were found. Similar observations were made with kidneys. This new evidence makes Prinzmetal's conclusion equivocal.

Examination of pulmonary veins, left heart, aorta and spleen showed no beads in 142 animals, 2 in 10, 10 in 5 and from 200 to 500 in 3. Diameters ranged from 10 to 130 microns. Before concluding that these findings demonstrate pulmonary shunts such possibilities as forced passage of pulmonary capillaries or Thebesian veins must be experimentally excluded.

Serious criticisms can be brought against the evidence which purports to demonstrate arteriovenous anastomoses in normal lungs.

Evidence, Including in vivo Observations, Suggesting Mechanical Blockage Rather than Reflex Vasospasm as the Cause of Death in Pulmonary Embolization

William H. Knisely, John M. Wallace, M. Stephen Mahaley, Jr., and W. M. Satterwhite, Jr., Durham, N. C.*

We previously demonstrated in rabbits, cats and dogs that emboli injected into pulmonary or lobar arteries *only* caused death after retrograde flow caused generalized embolization of all lobes; no fatal "reflex" was initiated from 1 segment.

With the above, and this "syllogism" from clinical experiences in mind, that "although 1 pulmonary artery can be ligated under anesthesia, embolization of 1 artery while awake causes death," the following experiments were performed:

Fifty to 150 μ diameter glass beads were injected via ear or jugular veins into rabbits treated as follows: awake (15); awake plus 5 mpk C6 (2); pentobarbitalized (15); deeply pentobarbitalized plus oxygen insuffiation which abolished respiratory movements (5); same, plus thoracotomy, lung studied microscopically (30); and same plus 5 mpk C6 (2).

Only 1 animal died from less than 0.20 mpk of emboli, while only 1 survived 0.25 mpk.

In vivo observations were made before, during, and after injections. Following bead injections linear rates of flow increased instantly in unembolized arteries, which dilated causing increased volume of flow in them. Diameters of arteries reduced peripheral to emboli *if* no flow entered from adjacent capillaries. Precipitate formed on beads and "grew" upstream, blocking more vessels. No effect was observed from C6 itself, nor by it upon the events of embolization.

Four pentobarbitalized and 4 awake rabbits survived 1.0 gpk beads injected in small increments over weeks.

Because generalized embolization is necessary for death, and approximately the same amount of beads killed all animals, and no general or local vasospasm was ever seen, and beads were not toxic per se, we conclude: mechanical blockage alone is sufficient to explain death in these animals.

We suggest that the small arteries of supposedly unembolized portions of lungs be carefully examined before any reflexes from embolized arteries are invoked explaining sequelae of embolization.

Mechanical Factors in Rupture of the Heart

Robert M. Kohn, Buffalo, N. Y.

Previous studies on cardiac rupture as a complication of myocardial infarction have suggested that elevation of intraluminal pressure, as with hypertension or increased physical activity, is an important factor in its pathogenesis. An analysis of cardiac ruptures shows that other mechanisms may also be operative. These possibilities were explored in latex analogs of heart chambers.

At least 2 discrete mechanisms bring about rupture in such analogs. Acute rupture results if the pressure or volume be increased beyond the elastic limits of the material. Under these conditions, the wall is stretched and thinned, an aneurysm is produced, and the rupture, usually T-shaped, splits almost the entire length of the dilated segment, and also shears at 1 or both junctions with the undilated segments.

A second form of rupture results from a "fatigue" effect, which develops after the elastic chamber has been dilated and contracted many times. The rupture here occurs at lower pressures and volumes than the vessel was able to withstand earlier. This effect is enhanced if the wall of the chamber is damaged in any way. This type of rupture produces a relatively small hole.

The occurrence of rupture in any particular cycle

or at any particular pressure or volume is unpredictable. Static stress-strain experiments shed no light on the appearance of this type of rupture.

Rupture of infarcted muscle may represent either a bursting or, more often, a "fatigue" effect. Factors to be considered in rupture of an infarct include the altered elastic and rheologic properties of the infarcted area, the pull of the uninvolved wall, the systolic increase in the radius of the infarcted area with accompanying increased tension, and dissection by a jet of blood. Intracavitary pressure is probably of lesser importance. Exertion and hypertension may contribute not so much by increasing pressure as by causing dilatation of the heart or increase in the rate.

Dietary Protein: A Factor Which May Reduce Serum Cholesterol Levels

Mohan G. Kokatnur, Nissan T. Rand, Fred A. Kummerow, and Harold M. Scott, Urbana, Ill.

Approximately 1,500 day-old chicks of known genetic strain were used in 3 different series of experiments to determine the effect of variations in dietary protein on serum cholesterol levels. Three replicates of 10 birds each were fed the test diet for a 4-week period. The basal diet contained a protein mixture of casein, soybean (Drackett) protein and gelatin, carbohydrate (Cerelose) and all of the essential growth factors. In the first series, 0, 10, 20 or 25 per cent animal tallow was added to a diet which contained 15, 20, 25, 35 or 45 per cent protein; in the second, 1 or 20 per cent corn oil was added to a diet which contained 20, 30, 40 or 50 per cent protein; and in the third, 0.1 or 0.3 per cent cholesterol was added to 1 or 20 per cent corn oil. The tallow or corn oil was added at the expense of the carbohydrate. A record of feed consumption was kept and the birds were weighed at weekly intervals. At the end of 4 weeks the birds were bled via heart puncture and the total serum cholesterol determined by the Sperry-Schoenheimer method.

The results indicated that the level of serum cholesterol was significantly lower at the higher dietary protein levels. The latter was more important to serum cholesterol levels than the level of dietary fat or the presence of moderate amounts of dietary cholesterol. Furthermore dietary fat appeared to lower serum cholesterol at a given protein level. For example, at a level of 1 or 20 per cent corn oil and 20 per cent protein, the serum cholesterol value averaged 194 and 161 mg. per cent, while on 50 per cent protein it was 114 and 105 mg. per cent respectively.

Dietary fat may actually be needed in the metabolism of exogenous cholesterol as the serum cholesterol was higher in birds kept on .3 per cent cholesterol and 1 per cent corn oil than in those on .3 per cent cholesterol and 20 per cent corn oil.

Electric Ventricular Defibrillation: The Relationship Between Epicardial Burns and Late Mortality

Allan B. Kortz and Henry Swan, Denver, Colo.

During recent experimental studies of ventricular fibrillation in hypothermia (24–26 C., rectal), 32 dogs underwent bilateral, transsternal, thoracotomy and right ventriculotomy. Of these, 16 developed ventricular fibrillation sometime during the procedure. Electric defibrillation was successful in 15 animals. However, 11 of these died during the 7-day "survival" period: a "successful" defibrillation of 95 per cent; a late mortality of 73 per cent. Human patients who have been "successfully" defibrillated on our service have demonstrated a high, late, mortality also. All of the 16 dogs who had not fibrillated were alive and well 1 week postoperatively: a mortality of 0 per cent.

In the operating room and laboratory defibrillation has been attempted by placing the bare defibrillation electrodes upon the heart and applying 170V–220V for 0.13 sec. from base to apex. Epicardial burns have been noted on many human and canine hearts following the "successful" application of this technic.

To assess the relationship of these burns to the late postdefibrillation mortality, a series of dogs were defibrillated using the technic as described but with the defibrillator electrode faces covered with saline-soaked gauze, cottonoid, or felt. Of 10 animals so treated all were successfully defibrillated and 9 were alive and well 7 days later: a successful defibrillation of 100 per cent; a "late" mortality of 10 per cent.

Covering the defibrillator electrode faces has been described during recent decades as a means of improving conduction through the heart and affording protection against epicardial burns. However, there is no unanimity of opinion among cardiac surgeons regarding its adoption or importance. Most commercial defibrillators are distributed without covering for the electrode faces or suggestions for its employment. We have found no other objective study which indicates the relation of epicardial burns to the ultimate survival of the patient.

Electrocardiographic tracings and histologic data pertinent to this study will be presented.

Dissecting Hematoma Due to Giant Cell Aortitis: Report of Two Cases and the Consideration of a Systemic Disease, Giant Cell Arteritis

Sidney O. Krasnoff and Henry Brody, Philadelphia, Pa.

Two cases of dissecting hematoma are described. The diagnosis was made at autopsy. One case was that of a 53-year-old Negro male, and the other an 87-year-old white female. Both patients died following rupture into the pericardial cavity. Histologic

studies demonstrated a characteristic inflammatory lesion of the outer media, with multinucleated giant cells in some areas. This process was not restricted to the aorta, but also was demonstrated in many of the major arterial beds including the renal and coronary vessels. The similarity to the cases of giant cell aortitis originally described by Sproul and Hawthorne, and by Gilmour, is pointed out. The relationship to temporal arteritis is discussed. In an extensive search of the literature only 2 previous cases of dissecting hematoma could be found in which this entity was considered as the causal factor. This report adds the third and fourth cases to those previously reported, 1 by McMillan and the other by Margery.

Management of Peripheral Arterial Embolism

Raymond J. Krause and John J. Cranley, Cincinnati, Ohio.

Peripheral arterial embolism is a prime example of a true "medicosurgical" emergency. Proper treatment demands full use of both medical and surgical therapeutic measures. It is believed that the basic pathology is twofold, consisting of the embolus itself and distal thrombosis. The latter is usually the determining factor in survival or loss of limb. That is why initial use of heparin is important, offering the patient some immediate protection while preparations are being made for surgical intervention. Removal of the embolus and re-establishment of arterial continuity constitute one of the most acute surgical emergencies. In reported series approximately 85 per cent of successful embolectomies are performed within 6 hours; however, recent experience suggests that this time limit may be extended, and we now recommend surgical removal as long as the limb is viable.

The concept of arterial spasm playing a major role is rejected. It is rather the distal propagation of the clot that is the determining factor in loss of limb. Postoperatively, the use of anticoagulant therapy is essential to prevent further embolization and this in itself is contraindication for the use of sympathetic blocks.

Experiences with 29 peripheral emboli occurring in 24 patients are reported. Seven patients were seen too late for specific therapy; in this group there were 4 deaths and 4 amputations. Four patients were treated with anticoagulant therapy alone, resulting in 2 deaths and 2 therapeutic successes. Fourteen patients having 17 arterial emboli were treated by embolectomy in conjunction with anticoagulant therapy. In this group there were 3 deaths and 3 amputations. The most encouraging aspect is the fact that it was possible to remove successfully 5 of 7 peripheral arterial emboli more than 12 hours after they had lodged.

An Evaluation of the C-reactive Protein and S-GO Transaminase Determinations in Coronary Artery Disease

Irving G. Kroop and Nathan H. Shackman, Brooklyn, N. Y.

C-reactive protein (CRP) and S-GO transaminase were compared in 22 patients with transmural infarction and in 57 patients with symptomatic coronary disease without Q waves, i.e., coronary insufficiency. The latter group included 25 patients without significant myocardial necrosis and a negative CRP, and 32 patients with necrosis and a positive CRP. Statistical analysis of our results confirm the findings of LaDue. The transaminase levels in the transmural infarction group were consistently elevated early in the disease. The mean of the levels in coronary insufficiency with necrosis was significantly elevated when compared to the normals (60 cases) and to coronary insufficiencies without necrosis (25 cases). However, the wide range (19–46 units/ml.) in the latter 2 groups without necrosis and the many equivocal, high-normal values in CRP positive coronary insufficiency with necrosis (22 out of 32) limit the application of the transaminase test in the milder case of myocardial necrosis.

Both CRP and transaminase were abnormal in 11 patients with necrosis. However, serial determinations of both tests in selected instances of unequivocal necrosis indicate that the degree of necrosis sufficient to form CRP may not release enough total enzyme to elevate the serum transaminase concentration beyond the normal range. The time-lag from beginning necrosis to securing the blood sample is another limiting factor in these mildly ill patients with necrosis. They are usually seen days after onset of symptoms when transaminase may be normal. The nonspecific CRP may be detected more readily at this later time because its formation depends on the inflammatory response to necrosis and not on the earlier liberation of enzyme.

The limiting factor of the more sensitive CRP determination is its nonspecificity. All extracardiac stimuli for its formation must be absent before it can be employed clinically. With limitations defined, both tests may be helpful in the diagnosis of myocardial necrosis.

Effect of Acute Unilateral Pulmonary Artery Occlusion on the Pulmonary Blood Volume in Dogs

Hiroshi Kuida, Boston, Mass., Paul Novack, Boston, Mass., Elliot Rapaport, Albany, N. Y., Florence W. Haynes, Boston, Mass., and Lewis Dexter, Boston, Mass.*

The effect of acute unilateral pulmonary artery occlusion on the pulmonary blood volume was studied in intact, anesthetized dogs. A catheter with

an inflatable balloon was positioned so that a main branch of the pulmonary artery could be completely occluded. A single-lumen catheter used for obtaining pressures and for injection of indicator, was placed in the right ventricle with the tip immediately proximal to the pulmonic valve. Cardiac output (CO) and so-called pulmonary blood volume (PBV) were measured by the indicator-dilution method of Stewart and Hamilton. Eleven studies were performed on 10 dogs. Right ventricular (RV) and femoral arterial (FA) pressures, CO, and PBV were measured before and 10 min. following unilateral occlusion.

The average values during the control and occlusion periods of the various parameters measured and the percentage change were as follows: RV systolic pressure (mm. Hg) 26 to 29, (+12 per cent); FA mean pressure (mm. Hg) 151 to 147 (−3 per cent) CO (L./min.) 3.6 to 3.9 (+8.3 per cent); PBV (ml.) 424 to 385 (−9.2 per cent). During the control period, the vascular volume of and blood flow through 1 lung represented approximately half of the totals measured. During occlusion, however, the total flow and volume represented that of only 1 lung, and since the total values for flow and volume did not change dramatically, it is apparent that both the flow and volume in the unoccluded lung approximately doubled with only minor changes in pressure. The good correlation between flow and volume through 1 lung (r = +.98) appeared to be linear within the range of values measured. These studies confirm similar findings in other situations, and is suggestive that this relationship between pulmonary blood flow and volume is an important physiologic mechanism interrelated to the relationship between pressure and flow and pressure and volume.

Effects of Lipemia on Tissue Oxygenation in Arteriosclerosis Patients

Peter T. Kuo, Philadelphia, Pa.*

It has been observed that fat infusion causes a drop in the oxygen tension of the dogs myocardium. and that postprandial lipemia precipitates angina pectoris in patients with severe coronary artery disease. Consequently, studies were made to determine whether the successful control of lipemia would actually improve the signs and symptoms of coronary and peripheral arterial insufficiency.

Ten atherosclerotic patients (6 with idiopathic hyperlipemia and 4 with high and prolonged lipemia following fat ingestion) were given 30–45 Gm. of sitosterol and a diet of 15–20 Gm. of fat per day. In 7 cooperative patients, serum cholesterol, phospholipid and total esterified fatty acid levels fell to nearly normal levels 8–12 weeks after the treatment had begun. These lipid levels were maintained for periods from 4–24 months.

Three young hyperlipemic males had effort angina and a positive electrocardiographic test with exercise. All 3 were free from anginal pain with a negative electrocardiographic test 3–6 months after the start of the therapy. Two patients with peripheral arterial disease and intermittent claudication showed a progressive increase in the standardized claudication time soon after the control of the hyperlipemia. Coincident with the increase in claudication time, a progressive improvement of the skin temperature readings with vasodilatation test was also observed. Two patients with both coronary and peripheral atherosclerosis had very abnormal ballistocardiograms with very low and bizarre ballistic complexes. Subjective improvement and a significant increase in the amplitude of the ballistic waves were noted 6–8 months following therapy.

Three patients in this group who made only token efforts to cooperate showed neither a significant lowering of the blood lipids, nor any improvement in the symptoms and signs of arterial insufficiency.

Further study on a larger series of patients is indicated.

Induced Cardiac Arrest as an Adjunct in Intracardiac Surgical Procedures: An Experimental Study

Conrad R. Lam, Thomas Geoghegan, Alfredo Lepore, and Charles K. Sergeant, Detroit, Mich.

In a previous communication (J. Thoracic Surg. **30:** 620, 1955) we reported that the heart of the normothermic and hypothermic dog could be stopped by the intraventricular injection of potassium chloride and then restarted following cardiotomy. Resuscitation was accomplished by cardiac massage, and countershock for the ventricular fibrillation which was regularly encountered.

Potassium chloride was used to arrest the heart in an additional series of 20 animals under hypothermia and ventricular septal defects were repaired with a patch of teflon. The excess potassium solution in the left ventricle was removed by lavage through the experimental defect before its closure. Resuscitation was much easier than in the earlier series, and was accomplished in all of the animals. Three died in the postoperative period. In a control series of 12 animals in which the heart was allowed to beat during the operations, resuscitation was not accomplished in 5. The others required many counter shocks.

Because ventricular fibrillation, although reversible, was common following cardiac arrest induced with potassium chloride, in November 1955 we began to use the drug acetylcholine. Sixty-four experiments were performed. Resuscitation was accomplished in 20 normothermic animals by either cardiac massage or perfusion of the coronaries with oxygenated blood. In a series of 37 hypothermic dogs, resuscitation was not accomplished in 5 due to improper filtration of the perfusion blood; all of 2 animals in which massage alone was used were

suscitated. Using the De Wall type of oxygenator to perfuse the aorta and coronaries, 7 out of 7 hearts were easily started.

Operations on the atrial and ventricular septa and the aortic valves were found to be exceedingly easy with the perfectly dry and still heart provided by induced cardiac arrest.

Clinical application of the method has been thought to be justified and it has been used on 6 clinical cases at the time of the submission of this abstract.

Persistent Ostium Atrioventriculare Commune: Hemodynamic Findings and Differential Diagnosis

Edward C. Lambert, William S. Webster, and Kornel Terplan, Buffalo, N. Y.

A review of the 288 major cardiac malformations found postmortem over a 20-year period at the Children's Hospital of Buffalo revealed persistent ostium atrioventriculare commune as a relatively common abnormality. There were 18 such cases (6 per cent) of the total cardiac anomalies seen. All of the deaths but 1 occurred in infants under the age of 2 years.

Analysis of the available clinical information on the 18 patients disclosed no features considered to be of diagnostic value in distinguishing this condition from other anomalies producing cardiac enlargement and increased pulmonary blood flow. Congestive heart failure was present in all. Murmurs were variable, ranging from loud to absent even on repeated examination. Cyanosis, while common, was present only with infection, on exertion or with congestive failure. Electrocardiogram findings were available on 8 patients. In 7 there was clear evidence of marked right ventricular hypertrophy.

Heart catheterization data on 5 of the patients who subsequently were studied at autopsy revealed: (1) Evidence of a large left-to-right shunt at the level of the right atrium in all; (2) essentially equal systolic pressures in the right ventricle and in a systemic artery in all; (3) ease of passage of the catheter into the left atrium with the finding of higher oxygen content in the blood sample obtained from this chamber than in the right atrium in 4 patients; and (4) passage of the catheter from the right ventricle directly into the aorta in 1 patient.

Marked thickening of the media in small and mid-caliber branches of the pulmonary arteries was present in all of the 5 patients who had been catheterized.

It is concluded that from a consideration of the frequency of the condition and the consistency of the catheterization findings, a persistent ostium atrioventriculare commune should be strongly suspected whenever the above combination of catheterization data is obtained.

Studies on Mechanism of Tolerance to Ganglion-Blocking Drugs

Herbert G. Langford and John Harbour, Jackson, Miss.

During the first month of therapy of hypertension with ganglion-blocking drugs the dose required to produce a given lowering of blood pressure may increase to 10-fold that initially required. This tolerance has been attributed to increased activity of a "nephrogenic" factor. To study another possibility, that of decreasing effect of the drug as an autonomic blocking agent, an independent measure of autonomic activity was desired. The effect upon a vagal function, accommodation (near-point) was chosen. Eleven patients with severe hypertension have been followed from 2 weeks to 3 months. Supine and standing blood pressures and near-point of the eye have been determined repeatedly, prior to and during ganglionic blockade therapy. In 10 out of 11 of the patients there was concomitant variation of near-point and blood pressure, with the near-point receding from the eye at the same time that the pressure is lowered. Then with increasing tolerance, both near-point and blood pressure tend to return to control values. If dosage is increased adequately to maintain blood pressure lowering, there will be no further change in near-point.

Because of the parallelism of 2 independently determined effects, both of which are mediated via the autonomic nervous system, we feel that the common factor in tolerance is decreasing efficiency of the drug in producing ganglionic blockade and not the increase of a "nephrogenic" component.

In addition, studies are under way to establish acute dose-response curves of blood pressure and near-point changes to i.v. administration of hexamethonium, pentolinium, Su 3088 (Ecolid), and mecylamine.

Evaluation of Operations for Coronary Artery Disease

David S. Leighninger, Cincinnati, Ohio.

During the past 21 years Beck has operated on more than 350 patients for coronary artery disease During recent years more than 50 surgeons throughout the world have operated on more than 1,000 patients, utilizing either the Beck operation or operations based upon the principles of the Beck operation. The principal mechanism of benefit from these procedures is the development of intercoronary arterial communications by the heart as the result of various stimuli.

Intercoronary communications resulting from these stimuli or various combinations of stimuli have been evaluated by the Mautz-Gregg backflow method. These studies show that the combination of stimuli known as the Beck operation—partial sinus ligation, mechanical abrasion of the pericardium and

epicardial surface of the heart, the application of 0.2 Gm. powdered asbestos—develops more intercoronary communications than do other stimuli, without morbidity and without mortality.

Other stimuli develop less intercoronaries, many of them with an appreciable operative mortality, postoperative morbidity, and occasionally with the production of chronic compression of the heart by scars.

Clinical experience with the Beck operation will be presented to show that the operation on patients carries a negligible operative mortality, significantly reduces pain and improves exercise tolerance in 9 out of 10 patients, and delays death.

Thromboangiitis Obliterans and Atherosclerosis: Part II

Irving Leinwand, A. Wilbur Duryee, and Maurice N. Richter, New York, N. Y.

The records of patients admitted to the University Hospital during the past 16 years with a diagnosis of thromboangiitis obliterans were reviewed and pathologic material re-examined. Of 80 patients, the clinical diagnosis was confirmed by the pathologist in 3 cases; 1 by biopsy, 1 by examination of several amputated fingers, and 1 by mid-thigh amputation. In 5 other patients with mid-thigh amputations, 2 with amputated toes, and 2 with laparotomies after attempted thrombectomies, the diagnosis was arteriosclerosis or atherosclerosis. In 1 of the laparotomies, a successful arterial transplant was performed at the bifurcation of the aorta for thrombosis in an area of arteriosclerotic plaques. The graft however, perforated in both common iliacs at short intervals of time and the patient died. The graft had been secured from an 18-year-old male who had been stabbed to death. The sections taken at the blood vessel bank were normal. However, sections taken through the areas of perforation showed atherosclerosis. In 17 patients in this series who did not have surgery, the clinical diagnosis of thromboangiitis obliterans was accepted as probably correct based on the presence of occlusive arterial disease with recurrent superficial thrombophlebitis, past or present, and/or involvement of the upper extremities, in the absence of diabetes, angina, myocardial infarction, or hypertension. In the absence of venous pathology, arteriography is indicated since surgical repair of segmental atherosclerosis may prevent loss of limb and possibly, life. Since 40 of these patients reviewed appeared to have had atherosclerosis, thromboangiitis obliterans is obviously not as common as one might assume from rather large series of cases reported in the literature. Certainly youth can no longer be considered prima facie evidence of thromboangiitis obliterans.

Comparison of Disability and Exercise Tolerance of Cardiac Patients Referred for Evaluation of Work Capacity

Robert M. Levenson, Donal R. Sparkman, and Robert A. Bruce, Seattle, Wash.

One hundred eighty-four cardiac patients have been referred to a Cardiac Work Evaluation Clinic primarily from private physicians for evaluation of physical ability and wisdom of returning to work. The majority had recently convalesced from a cardiac illness and the others were working with known heart disease. There were 166 men and 18 women ranging from 16 to 69 years of age.

Each was carefully studied from a multidisciplinc approach based on personal examination or interview of an internist, psychiatrist, social worker, and vocational counselor. The purpose was to determine disability due to cardiovascular and other clinical diseases, psychiatric disorders, socioeconomic factors, and adequacy of previous educational and vocational experience.

Exercise tolerance was evaluated by a standard procedure involving grade walking on a motor-driven treadmill. Symptoms, cardiorespiratory signs, blood pressure, and precordial lead electrocardiographic responses were noted. Endurance, respiratory efficiency and recovery heart rate were used to derive an estimate of exercise tolerance expressed as the physical fitness index (PFI).

Satisfactory correlations were obtained between the clinical estimates of disability expressed as functional capacity (New York Heart Association) and the physical fitness index in 70 per cent of the patients.

Twenty-five per cent showed a significant variation between the clinical estimate and PFI which was considered the more objective estimate. This occurred because patients were unable to describe their limitations or did not recognize them. The remaining 5 per cent had either limited themselves or been so severely restricted that it was not possible by history alone to make a satisfactory judgment of physical capacity.

It is concluded that objective testing of exercise tolerance provides a means of checking the accuracy of clinical appraisal of disability, and facilitates rendering sound clinical advice with respect to physical capacity for future employment.

Observations on Pulse Pressure Contour in the Lesser Circulation in Patients with Mitral Insufficiency

David C. Levinson, Morris Wilburne, and John P. Meehan, Jr., Los Angeles, Calif.

In the course of studying a number of patients with mitral insufficiency by cardiac catheterization an unusually shaped pressure curve was obtained

from the main pulmonary artery of some of the patients. The unusual feature of this curve is a second pressure peak on the diastolic limb of the curve that has a peak pressure equal to or greater than the true peak systolic pressure in the pulmonary artery. An examination of pressure tracings obtained from a series of stations between the main and wedged pulmonary artery positions indicate that the second pressure peak is the "V" (or regurgitant) wave of mitral insufficiency that has been transmitted in a retrograde manner to the main pulmonary artery.

The mean pulmonary arterial pressures were elevated throughout the pulmonary circulation. Using cardiac output data obtained by the conventional Fick method, a calculation of the pulmonary arteriolar resistance revealed a normal or reduced pulmonary vascular resistance. The data is interpreted as meaning an increase in the pulmonary vascular tone without a change in pulmonary vascular resistance. Such a set of conditions would favor the retrograde transmission of the "V" (or regurgitant) wave of mitral insufficiency in a retrograde direction and these conditions probably account for the appearance of the "V" wave in the main pulmonary arteries of the patients studied.

Effect of Smoking on Circulatory Measurements

Arthur J. Lewis and Walter Redisch, New York, N. Y.

Ballistocardiograms, electrocardiograms, extremity blood flow and surface temperature of normal individuals were evaluated following smoking. In each subject these tests were normal prior to smoking.

Forty-two healthy individuals (19 males; 23 females), age range 18–55 years, were tested after smoking a standard cigarette. They were encouraged to inhale, and to finish in 6 min.

Ballistocardiograms were obtained with a portable ballistocardiograph, recording displacement, velocity and acceleration. Electrocardiograms were taken with a direct writer. Recordings of surface temperature and lower extremity blood flow (utilizing plethysmography) were obtained in a constant temperature room at 25 C. Measurements were taken before and at 2, 6, 10 and 20 min. intervals, following the onset of smoking.

Ballistocardiograms were graded according to amplitude and form of complexes. Electrocardiograms were interpreted by standard criteria. Changes in blood flow greater than 2 ml./100 ml. tissue/min., and in surface temperature of at least 2 C. were considered significant.

Five subjects (12 per cent; age 24–48; 3 males, 2 females) had ballistocardiographic deterioration in acceleration. Two individuals (5 per cent; ages 24 and 42; 1 male, 1 female) had electrocardiographic changes. Nine subjects (21 per cent; age 18–55; 3 males, 6 females) had blood flow diminution. Six individuals (14 per cent; age 20–49; 4 males, 2 females) had a surface temperature drop.

Ballistocardiographic deterioration was always accompanied by a change in 1 of the other measurements; in 2 instances by electrocardiographic abnormalities, in 2 by surface temperature fall, and in 1 by diminished blood flow.

There was poor correlation between lowered skin temperature and diminished extremity blood flow, possibly because temperature was recorded from a glomus area, the toe, while leg plethysmography indicates mainly muscle flow.

No subject had changes in more than 2 measurements following smoking.

Studies in Intracardiac Phonocardiography

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This, as far as we know, is the first report of a new method for the detection of sounds from within the heart, the acoustic aspects of which were reported by the authors in June 1956 at the Second International Congress on Acoustics. These studies, which were carried out in dog and man, were made possible by the application to phonocardiography of acoustic technology developed for undersea warfare, and, specifically, by subminiaturization of probe hydrophone technics. The transducer is a hollow cylinder of activated barium titanate, a piezoelectric ceramid. Several types of catheters have been made incorporating this element, and both photographic and tape recordings made. From the tape, spectrograms have been run on the Kay Cardialyzer. With 1 transducer acting as a transmitter, pure tones have been introduced into the heart and transmission noted with a second catheter.

The first and second sounds are heard in all chambers and in the great vessels near the heart. In the dog, sounds are loudest in the left ventricle near the mitral valve. Left heart sounds in humans await completion of a catheter now being designed. The fourth sound is routinely heard in the right atrium, inconstantly in the right ventricle, and not in the superior vena cava or pulmonary artery. It is not heard in atrial fibrillation. A systolic murmur is present in the aorta and pulmonary artery even when not heard externally. In patent ductus, the machinery murmur which is heard in the pulmonary artery, and loudest at the ductus, disappears as the catheter is pulled back through the pulmonic valve into the right ventricle. Spectrograms indicate that the frequency range of intracardiac sounds is similar to that recorded externally. This technic shows promise of increasing knowledge of the genesis and transmission of sounds and murmurs, and, it is

hoped, will be a valuable adjunct in the diagnosis of valvular disease and intracardiac shunts.

Detection of Minimal Myocardial Infarction by Serum Enzyme Content

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With doubtful cases of clinical myocardial infarction, specifically those which present such minimal electrocardiographic changes as serial T-wave inversion, the following criteria are considered diagnostic: rapid erythrocyte sedimentation rate (ESR) and increased serum concentration of C-reactive protein (CRP) and/or glutamic oxaloacetic transaminase (SGOT). The most sensitive of these nonspecific tests as formerly reported is SGOT and a statistically determined minimal level of abnormality is 42 units/ml. The size of the infarct is a quantitative variable and so should be the concentration of SGOT at its lower levels. An intermediate zone between 32 and 42 units/ml. of SGOT is suggested to aid in the detection of minute lesions.

Studies were made in 64 cases of presumptive myocardial infarction of the clinical pattern, the WBC, ESR and the serum content of SGOT and CRP. In selected cases determinations were made of lactic acid dehydrogenase (LAD), a more sensitive enzyme, and serum glutamic pyruvic transaminase (SGPT), an enzyme more specifically reflecting liver damage. Control studies on 16 patients without heart disease demonstrated that food, bed rest and physical activity were found to have no influence on the serum content of these enzymes.

Seventeen patients had minimal clinical findings but exhibited Q waves and serial S-T segment as well as T-wave abnormalities. Fifteen had SGOT in the "abnormal" zone and 2 in the borderline zone (32–42 units/ml.).

Forty-six patients (48 attacks) had only serial T-wave inversion including 2 with observed secondary attacks. Nineteen were in the abnormal zone (over 42 units/ml.). Ten were in the "intermediate" zone and 19 in the normal zone. One patient with coronary disease but no infarction was in the "intermediate" zone.

On selected cases the LAD elevation appeared earlier than SGOT and persisted longer. SGPT was low relative to SGOT when no hepatic dysfunction was present and relatively high when the reverse occurred.

The use of an intermediate zone of SGOT content and of determinations of LAD and SGPT aid in diagnosis of minimal myocardial infarcts or those complicated by hepatic dysfunction. ESR and CRP correlate poorly with other diagnostic features in doubtful cases and occasionally may be negative with clinically and electrocardiographically well established diagnoses

Problem of Myocardial Aneurysm: Recognition and Treatment

William Likoff and Charles P. Bailey, Philadelphia, Pa.

Although myocardial aneurysms may result from congenital defects, trauma and syphilis, the majority develop following myocardial infarction. The incidence is estimated as high as 20 per cent in the autopsy population of these patients.

Ventricular aneurysm has a poor prognosis characterized by the persistence of angina, the development of intractable heart failure, embolic accident and sudden death.

In 1954, the authors reported the first successful excision of a ventricular aneurysm and suggested this procedure was capable of correcting the abnormal cardiac function arising from the lesion.

This communication reports the etiology, pathologic features, clinical manifestations, diagnostic methods, surgical management and results in 7 patients with myocardial aneurysm. Additionally, it reviews the remarkable progress noted in 1 patient 26 months postoperatively.

In 5 patients the "aneurysm" developed from 4 to 12 months after an extensive anterolateral or posterolateral myocardial infarction. In 2, it followed direct trauma to the left ventricle.

When secondary to myocardial infarction, the aneurysms averaged 4.5 x 6 x 5 cm., involved the anterolateral or posterolateral surface, and uniformly contained a mural thrombus. In this group, congestive heart failure and paroxysmal arrhythmias were the major clinical problems. Gallop rhythm was the only characteristic auscultatory finding.

Roentgen examination was the most consistent diagnostic aid. Roentgen-slit kymography and left angiocardiography proved especially helpful in ascertaining a full communication between the chambers of the ventricle and aneurysm.

An excisional procedure was used in each patient. Six of the patients recovered after surgery and, in these, compensation was restored, gallop rhythm corrected, and paroxysmal arrhythmias arrested.

From these experiences, it appears reasonable to suggest the surgical removal of a ventricular aneurysm except when it involves the septum, because of the inherent threat to life posed by the continuing lesion.

Subcutaneous Ossification in Chronic Venous Stasis

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Subcutaneous ossification of the legs is occasionally found in patients with chronic venous insufficiency and cellulitis, associated with long standing deep venous stasis or extensive varicosities.

Fourteen such cases, in various stages of develop

nent, were encountered in the past 5 years. In 4 of these, there was unilateral involvement. All patients were female. The age ranged from 48 to 69 years. Ten had recurrent ulcerations overlying ossified plaques, which in 2 required removal and skin grafting. Tissue ossification outside the legs was not found. Abnormal calcium, phosphorus, alkaline phosphatase and protein concentrations in the blood were not found. The x-ray picture was distinctive. Pathologic and histologic studies were not conclusive as to the pathogenesis of the condition.

Only 3 similar recognised cases were found in the literature, while extraskeletal ossification of different pathogenesis is described in poliomyelitis, paraplegia, muscle trauma, pulmonary stasis, postoperative scars, epitheliomas, sebaceous cysts, dermatorrhexis and other conditions. Some cases in the literature resembled cases in this group in their x-ray appearance but were interpreted differently; no pathologic studies were available in these cases.

The etiology of subcutaneous leg ossification is unknown. Ten of the 14 described cases were sewing machine operators, some only for a short period and many years prior to examination. The etiological significance of the occupational history is under investigation.

Resonance of Pulsating Fluids

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The circulation is subject to laws of hydraulics and laws of resonance. To study the effects of these 2 types of laws, they must be studied separately. To separate the effects of these 2 types of laws, pulsations are produced in tubes of fluid. At the proper frequency the pulsations become resonant or tuned. A lineal flow superimposed upon pulsations produces pulsating flow. Since the flow and pulsations are independently controlled, the system lends itself to analysis. In resonance, flow and pressure correspond. In dissonance, the pressure is excessive in relation to flow. There are 2 kinds of pressure in dissonance. One is real pressure which drives the fluid; the other is a useless ineffective pressure due to impedance. Impedance, as differentiated from resistance, is 1 of the characteristics of any dissonant system. In an electric system, it causes loss of efficiency, overloading of the lines, and strain on the generator. In a mechanical system, it causes loss of efficiency, excessive wear of the bearings, and vibrations. In a pulsating hydraulic system, impedance causes loss of efficiency, excessive pressure, increased impact on the conduit, and strain on the pump. The theory of resonance applies to the pulse waves of a hydraulic system in the same sense that it applies to the sound waves of a pipe-organ or to the mechanical vibrations of a machine. A low-pressure system in dissonance is subject to greater strain than a high-pressure system in resonance. According to this concept, the circulation is normally resonant, but in some disorders may become dissonant. Impedance due to dissonance may be a factor in hypertension.

Experimental Studies on the Stimulation of Collateral Blood Flow to the Myocardium

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In an attempt to stimulate collateral circulation to the myocardium, an artery, through which was maintained a continuous arterial flow, was imbedded into the myocardium.

In a series of 20 dogs, the internal mammary artery was dissected from its origin at the subclavian artery down to the level of the sixth or seventh intercostal space. The artery was divided at its origin and passed through a 4 cm. tunnel in the myocardium of the left ventricle between the anterior descending and the circumflex coronary arteries. The free cut end of the internal mammary artery was then anastomosed to the thoracic aorta.

The animals were studied after a period of from 6 weeks to 6 months. Backflow from the peripheral circumflex coronary artery, and survival time after ligation of the circumflex coronary artery, were recorded. The specimens were injected with suitable materials in order to study collateral vascular channels. Photographs and x-ray pictures were taken and histologic studies were carried out.

In 15 of the 20 dogs, the transplanted internal mammary artery was patent. The backflow from the peripheral circumflex coronary artery and survival time after its ligation were found to be the same as in the control group of animals. By injection technics and histologic studies, no communication could be found between the imbedded artery and the coronary artery system. However, a communication between the imbedded mammary artery and the coronary venous system was demonstrated in 3 instances. The presence of the arteriovenous fistula, which is assumed to be traumatic, did not increase backflow or survival time.

Hemodynamic Studies in Restrictive Pulmonary Disease

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Twelve patients, known to have pulmonary insufficiency due to diffusion insufficiency, were studied by detailed pulmonary function tests and cardiac catheterizations at rest and on exercise.

These studies indicate that destruction or resection of lung tissue results in a decrease in the pulmonary vascular reserve which eventually increases the pulmonary vascular resistance and pulmonary artery pressure. As is characteristic of diffusion insufficiency, the alveolo-arterial oxygen

gradient widens on exercise. This gradient bears a direct relationship to the ratio of pulmonary vascular resistance to pulmonary blood flow. However, when the pulmonary vascular resistance is fixed as a result of the anatomic changes, the gradient is in direct proportion to pulmonary blood flow. It is therefore concluded that the alveolo-arterial gradient is directly proportional to the time of contact between the pulmonary capillary blood and alveolar gas.

The elevated pulmonary vascular resistance causes an increase in right ventricular work, which is manifested clinically as cor pulmonale. The intravenous administration of hexamethonium decreases right ventricular work due to a decrease in pulmonary blood flow in the presence of a fixed vascular resistance. At the same time, the decreased pulmonary blood flow results in a prolongation of contact time and a diminution in the alveolo-arterial gradient. The patients therefore benefit in 2 ways, namely, a decrease in right ventricular work and an improvement in diffusion insufficiency.

Natural Course of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life. II. Prognosis with Special Reference to Morbidity

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Because preponderant medical opinion currently favors surgical intervention in chronic rheumatic heart disease, and since there is a paucity of control information on the natural morbidity of the disease, in this study a long-term appraisal is presented of a large percentage of those rheumatic cardiacs whose survivorship is analyzed in the previous paper.

It was found that the great majority of patients with merely mitral insufficiency and minimal or moderate cardiac enlargement were asymptomatic. According to the most commonly used surgical criteria for operability in mitral stenosis, the majority of such patients were minimally disabled (class I). A fair number of these had concomitant aortic murmurs. The remainder were in classes II, III and IV, with a higher proportion of aortic involvement. Patients were excluded from surgical classification who had significant aortic pathophysiology. Most patients in classes II, III and IV had considerably enlarged hearts. Duration and changes in morbidity were analyzed for the entire group. Patients who appeared to develop objectively diminished cardiac reserve usually did so toward the beginning of the third decade of life.

The natural morbidity experienced by patients with rheumatic heart disease should be considered in the selection of candidates for surgical intervention.

Evaluation of Cholesterol and Lipoprotein Measurements as Indices of Atherogenesis

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The hypothesis that coronary heart disease is associated with elevation of the serum lipoproteins of the S_f12–20 and S_f20–100 classes has been tested by comparing these measurements, as well as the serum total cholesterol, for 1,974 well adult subjects with those for 273 patients with established evidence of coronary heart disease.

Each measurement showed great variability within each age and sex group. The cholesterol levels showed no significant trend with age for men after age 30 although a notable age trend in women was found. Young women have lower and women over 60 years have higher cholesterol levels than do men of the same age.

Groups of men with definite myocardial infarction showed higher mean levels of both cholesterol and lipoproteins than did well men. The level of serum cholesterol was a somewhat better index of the presence of coronary artery disease, especially in younger men, than were either of the lipoprotein measures. All 3 measures showed poorer discrimination between sick and well persons with increasing age.

The lipid measurements in 23 women with histories of myocardial infarction were similar to those of men with myocardial infarction. Two-thirds of these women were past 50 years of age. The lipid measurements of 141 men with definite angina pectoris were intermediate between those of well men and of men with myocardial infarction. The lipid measures were thus of even less predictive values for this disorder.

The significant elevations of the cholesterol and lipoprotein levels in persons with coronary artery disease indicate that this disease is associated with a disorder of lipid metabolism. However, the small size and large variance of this difference between sick and well persons seriously limits the clinical utility of the measurements in diagnosis or prediction. No combination of the 3 measurements could be found which greatly increased the separation between the sick and well groups over that provided by cholesterol alone. The cholesterol measure is recommended as a simple, reliable procedure for identifying people with the gross disturbances of lipid metabolism which often lead to coronary artery disease.

Myocardial Revascularization: Experimental and Clinical Critique and Preparation of Chronic Coronary Insufficiency in the Dog

Emmanuel Marcus, Ellsworth E. Hasbrouck, and Samuel Wong, Chicago, Ill.

Myocardial revascularization in properly selected cases has been observed to produce clinical improve-

ment. The cases selected are those with proved myocardial infarctions and/or status anginosis. We have attempted to find the physiologic and anatomic reasons for the observed improvement in laboratory animals. We have demonstrated a rather marked increased lushness of the deep myocardial arterial vasculature following coronary sinus ligation. Corrosion-injection specimens with vinyl plastic are exhibited of normal dog hearts, those subjected to multiple twig ligations, and of those subjected to coronary sinus ligation. Control ligations of the anterior descending coronary artery as a test object (challenge) are found to have a lower mortality rate than reported in the literature. The importance of determining the position of origin of the septal arteries is emphasized. It is concluded that although some anatomic evidence for the benefit of coronary sinus ligation is available, physiologic evidence is hard to come by because the normal dog heart is not a good test object for revascularization.

For the above reason, animals are now being made to simulate chronic coronary insufficiency of the human. This, by embolization of the coronary arterial tree with plastic spheres (method of Owens, Balchum and Swan) and then running the animals on the treadmill. It is believed that such a test object will better assess the value of any revascularization procedure.

Coexistence of Patent Ductus Arteriosus and Aortic Valvular Disease

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Patent ductus arteriosus as a rule exists as an isolated congenital anomaly in the noncyanotic patient. The coexistence of PDA and aortic valvular disease has been rarely reported in the American literature. The incidence as given in the larger series (3 out of 412 patients by Gross and Longino) seems inordinately low.

This report is presented to indicate the criteria for diagnosis and the clinical complications in 7 patients out of 50 operated for PDA in whom an aortic valvular lesion, presumably congenital aortic or subaortic stenosis, was present. This was confirmed by clinical findings, diagnostic carotid artery pulse tracings and, in 1 case, by postmortem examination.

Of the 7 patients, 5 were diagnosed preoperatively as having an associated aortic valvular lesion. In addition to the typical murmur of PDA with maximal transmission toward the left shoulder, the systolic and/or diastolic murmur assumed a different quality as they were traced to the aortic area. Two of these patients showed evidence of left ventricular enlargement out of proportion to the size of the shunt as estimated by clinical findings. In 1 patient the existence of aortic valvular involvement was not recognized until recovery from operation when a persistent aortic systolic murmur with diagnostic carotid pulse tracing was found. One patient was not seen until 1 year after her PDA had been ligated. This had been followed by subacute bacterial endocarditis on the aortic valve causing rupture of a cusp with severe aortic insufficiency, eventually causing her death.

Three of the 7 patients developed subacute bacterial endocarditis on the aortic valve. The presence of this associated congenital anomaly is, therefore, of more than academic interest.

It is concluded that a high level of suspicion for coexisting aortic valvular disease be entertained if the auscultatory findings do not conform to the original description of Gibson given over 50 years ago.

Endocrine Influences in Myocardial Infarction

Jessie Marmorston, Harry Sobel, Olive Hoffman, Jack J. Lewis, and Jacob L. Bernstein, Los Angeles, Calif.

The cyclic woman is apparently endowed with certain qualities which protect her against myocardial infarction. Following the menopause she becomes susceptible to this condition. An investigation was undertaken in order to determine if myocardial infarction in postmenopausal women is correlated with disturbances in endocrine activity. Studies were carried out on approximately 250 postmenopausal women who were classified by clinical criteria as (1) controls, and (2) myocardial infarction. The subjects ranged in age from 45–85 years. The average age of each group was approximately 60. The harmonic mean of the ketosteroid excretion was 5.22 mg./day for the controls, and 3.70 for the infarct group. The latter differed significantly from the control group. The corticoid excretion for the 2 groups was 6.39 and 5.31 mg./day respectively. As before, the controls and infarct group differed significantly from each other. The excretion of biologically active estrogen was .477 μg./day for the control group and .307 μg./day for the infarct group. The estrogen excretion of the infarct group was significantly less than the control group. The data would seem to indicate that a specific deficit of estrogen excretion exists in patients who have had a myocardial infarction. The serum protein-bound iodine was virtually identical in both groups (5.51 and 5.52 μg. per cent, respectively). The serum cholesterol levels were 272 and 279 mg. per cent respectively, and the serum phospholipids were 276 and 283 mg. per cent respectively. Results of similar investigations in men will also be reported.

Blood Pressure in Apparently Healthy People Sixty-Five and Over

Arthur M. Master, Richard P. Lasser, and Harry L. Jaffe, New York, N. Y.

The level of the mean blood pressure and frequency distribution curves, according to age and

sex in apparently healthy people aged 65 and over were determined. Information was gathered through questionnaires completed by about 4,000 physicians distributed throughout the United States.

15,396 cards were received. To insure that the data would be reliable, numerically adequate, and applicable to the entire white population of the United States, a group of 2,996 males and 2,756 females, fulfilling the following qualifications, were selected for statistical analysis: (1) Various geographic areas, rural and urban localities represented; (2) subjects ambulatory, noninstitutionalized; (3) extensive medical information available on each; (4) subjects with apparent cardiovascular disease excluded.

Blood pressure data obtained represents that observed in physician's office, viz. "causal," not "basal" pressure.

Significant observations were:

1. A wide range of blood pressure was compatible with apparent good health.

2. Average systolic pressures no longer continued to rise with age in males after 65, nor in females after 70–74. They remained constant to 85 and then declined. Females exceeded male pressures by 14 mm. Hg at age 70–74, but over the age of 90 the values approached each other. This may bear a relation to the fact that sex mortality rate differences begin to disappear at 90.

3. Diastolic pressure showed no sex difference and declined slightly after 85.

There was insignificant variation according to height, geographic location, occupation, rural and urban inhabitation. Relationship to weight will be reported.

Calculations were made from cumulative frequency curves and from the means and standard deviations of the blood pressure range which would include the central 80 per cent, 90 per cent and 95 per cent of observations. The significance of these values with reference to the range of "normality" in the average "apparently healthy" population will be discussed and will be compared with younger groups 16–44, 45–64.

ACTH and Steroid Therapy of Nephrotic Syndrome in Children and in Adults

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One hundred fifty cases of nephrotic syndrome (110 in children and the remainder in adults) have received 100 or 200 mg. of ACTH daily for a minimum period of 4 weeks while maintained on a low sodium–high potassium diet, antibiotics, iron, and vitamins.

A remission was obtained either during or following therapy in all but a few of the children. In the adults albuminuria disappeared in 20 per cent of the patients during the initial treatment course or subsequently on intermittent maintenance therapy. In the children on continued therapy the expected rise in serum total CO_2 content and fall in serum potassium and chloride levels were observed. Serum albumin rose toward or to normal; this was also true of the globulin when initial values were abnormally low. Blood sugar tended to rise while serum inorganic phosphorus fell. Cholesterol concentrations declined. NPN when elevated tended to return to normal. Serum sodium remained unchanged except when hyponatremia developed as a result of extrarenal sodium losses. In the adults the biochemical changes observed were less marked or absent. In both groups the urinary 17-ketosteroid output rose significantly, reaching values as high as 140 mg. in 24 hours.

The most serious of the side effects was the development of hyponatremia with convulsions in 4 patients; emotional disturbances were noted occasionally in the adults during the latter part of the therapy.

Seventy per cent of the children have remained well following the initial treatment course for periods up to 4 years in length. Recurrences up to 7 in number have appeared in the remaining 30 per cent. These have responded to retreatment. Intermittent therapy—3 days on ACTH or steroid and 4 days off—have decreased recurrences. In the adults remission has been followed by recurrence unless the patients have been placed on maintenance therapy.

Interactions of Mucopolysaccharides and Some Protein Components of Connective Tissue

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Sodium chondroitin sulfate (SCS) is present in hyaline cartilage in the form of a SCS-protein complex (SCS-P). Amino acid analyses show the protein moiety to be distinct from collagen. The mode of linkage of mucopolysaccharide and protein is unknown and may include covalent as well as electrostatic bonds. The SCS-P molecule approximates a rod-like structure of molecular weight near 5×10^6, 3800 Å long with a variable diameter depending upon the ionic environment. Higher molecular weight states up to 25×10^6 of SCS-P are also found. Experimental data suggest that the larger particles are formed by lateral aggregation of the smaller rod-like units described above, with the participation of small amounts of additional protein. Electrophoretic studies show that reversible complexes are formed at neutral pH between the acid mucopolysaccharides, SCS, sodium hyaluronate, heparin and soluble collagen or "neutral-soluble" collagen. The appearance of the complex is governed by the ionic strength of the medium and the molecular weight of the mucopolysaccharide. This result indicates that electrostatic forces are mainly responsible for the stability of the complex. Interaction between SCS-P and soluble collagen results

n gelation, which may be conditioned by the linear onfigurations of both interactants. The intercellular omponents of connective tissue (specifically cartilage) may be viewed as an ionic network gel. It is uggested that the state of this system, in particular he degree of swelling (following a theoretic nterpretation due to P. J. Flory, "Principles of Polymer Chemistry," Cornell University Press, 953), will be largely determined by a balance chieved between osmotic expansive forces due to mall mobile ions and cohesive or retractive forces rising from interactions between acid mucopolyaccharides, collagen, and noncollagenous proteins.

Tetralogy of Fallot

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The tetralogy of Fallot is a common occurring lesion that is perhaps the most familiar of all cyanotic congenital cardiovascular anomalies. The successes of corrective cardiac surgery have caused a heightened interest in congenital heart disease and this has resulted in the accumulation of a considerable body of clinical and physiologic data in patients with the tetralogy. This greater experience has brought about the realization that the original concept of the lesion as a single, fairly narrowly limited entity is no longer valid. The tetralogy can now be shown to occupy a broad spectrum in the field of congenital cardiac disease presenting in many forms. Thus, the variations of the tetralogy can masquerade as a ventricular septal defect with a left-to-right shunt, or present a picture of isolated valvular or infundibular stenosis.

The complexity of this spectrum is due to the varying degrees of severity of the component lesions and can be understood only by the recognition of the dominant hemodynamic features.

It is considered that the pulmonary stenosis and the ventricular septal defect are the essential defects of the entity. Dextroposition of the aorta is believed to be of less importance and is frequently more apparent than real.

Evidence will be presented that the presence of a ventricular septal defect and apparent over-riding of the aorta does not necessarily result in equalization of pressures in the left and right ventricles.

The present report consists of an effort to define the varying forms of the tetralogy on the basis of variation in the size of the ventricular septal defect and the severity of the pulmonary stenosis. A classification will be described and patients studied at this center will be presented as examples. The different forms of corrective surgery will be evaluated for each category.

‡ Deceased.

III. Cerebral Vascular Disease: Ten-Year Experience with the Use of Anticoagulants in Certain Cerebral Vascular Syndromes

Ellen McDevitt, Barbara M. Wright, Stefan Carter, William T. Foley, and Irving S. Wright, New York, N. Y.

In 1946 the first report by Wright and Foley on the use of anticoagulants in the treatment of recurrent cerebral emboli associated with rheumatic heart disease appeared. Since then increasing recognition of the usefulness of this form of therapy for the treatment of thromboembolic conditions of the cerebral blood vessels has been manifest. The necessity for careful differentiation between certain types of cerebral vascular disease is no longer academic and there has been a revival of interest in diagnostic technics. Newer methods of localization of lesions are being devised and utilized.

Patients with cerebral vascular disease on the basis of recurrent cerebral emboli, cerebral arterial occlusion including thrombosis and insufficiency of the basilar or internal carotid arteries have been treated with anticoagulants.

The present report is concerned with experience in treating such patients with anticoagulants over a 10-year period, and also includes the effects of such therapy on the long term outlook for these patients.

It is apparent in this study, as in earlier reports, that in these patients interrupted anticoagulant therapy is less efficacious than continuous therapy. The contraindications for anticoagulant therapy are the same as in the treatment of thromboembolic disease elsewhere in the body. Present indications for the use of anticoagulant therapy for cerebral vascular disease are considered to be: 1. Recurrent peripheral or cerebral emboli in the presence of rheumatic heart disease or arteriosclerotic heart disease with or without atrial fibrillation. 2. Cerebral arterial thrombosis including basilar or internal carotid artery thrombosis. 3. Intermittent basilar or internal carotid artery insufficiency. 4. Preparation of patient with rheumatic heart disease for cardiac surgery.

A summary of 10 years experience with the use of anticoagulants in the treatment of selected cerebral vascular diseases is presented.

Drug Therapy in Primary Hypertension Guided by Digital Circulatory Testing

Milton Mendlowitz, Albert D. Parets, Theodore Gold, and Stanley R. Drachman, New York, N. Y.

One hundred and twenty-seven patients with primary hypertension were observed under treatment with drugs administered singly or in various combinations over periods varying from 1 month to 3 years. The drugs used were *Rauwolfia serpentina* derivatives, including crude root, alseroxylon fraction, Reserpine, rescinnamine and recanescine; veratrum derivatives, including various veratrum

extracts and protoveratrine; hydralazine hydrochloride; and both orally and parenterally administered ganglion blocking drugs, including hexamethonium, pentapyrolidinium, chlorisondamine and mecamylamine salts. In 61 of these patients, digital arterial blood pressure and digital blood flow were measured prior to therapy: (1) under standardized conditions at room temperatures between 26 and 29 C., and (2) after inhibition of sympathetic nerve discharge by indirect heat supplemented by the intravenous administration of 0.8 mg./Kg. of 2,6-dimethyl-1,1-diethyl piperidinium bromide (SC 1950). From these data radius equivalents of the digital blood vessels in the constricted and dilated states and the work of vasoconstriction were calculated. In 15 of these patients, these studies were repeated during drug therapy and in 7 of the latter repeated again during treatment with placebos.

The extent of the decrease in intrinsic digital vascular caliber as measured by the radius equivalent during vasodilatation was a good index of the severity of the disease and was well correlated with the clinical evaluation. Sixty per cent of the patients treated responded with significant decreases in blood pressure and the correlation between the decrease in the work of digital vasoconstriction and response to therapy was good. Failure to respond occurred most frequently in patients in whom little or no neurogenic vasoconstriction could be demonstrated prior to treatment. In some cases, however, it occurred because of inadequate therapy. The circulatory test served as a guide to the adequacy of treatment and as a caution against overtreatment. Blood pressure levels alone were unreliable in these respects.

Influence of Posture on Renal Function in Heart Failure

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Changes in renal function similar to those in heart failure can be produced acutely in normal subjects by the passive erect posture. Since the effect of the passive erect posture in patients with heart failure is unknown, 18 patients with chronic cardiac decompensation were studied before, during and after a 30 min. interval of being tilted at 60 degrees. The urinary volume, clearance of inulin, clearance of para-aminohippuric acid, urinary sodium and potassium excretion and blood hematocrit determinations were made.

The mean figures of all patients show that the urinary volume fell from 4.6 to 1.6 ml./min. (65 per cent fall); the C_{inulin} fell from 67 to 43.6 ml./min. (34 per cent fall); the C_{PAH} fell from 237 to 180 ml./min. (24 per cent fall); the urinary sodium excretion fell from 114 to 52 mM (54 per cent fall) while the urinary sodium concentration rose from 21.61 to 29.70 M/L. (36 per cent rise); the urinary potassium excretion fell from 58 to 37 mM (36 per cent fall) while the urinary potassium concentration rose from 22.93 to 28.88 M/L. (20 per cent rise). There is a close correlation between the fall in C_{inulin} and urinary volume per minute. (R = +0.897 S.E. $\pm$ 0.1291 p = 0.001). There is no significant correlation between changes in C_{inulin} and C_{PAH} with changes in sodium excretion. This lack of correlation coupled with the rise which occurs in the concentration of the cations in the urine indicates that tubular reabsorption is the primary determinant of the amount of sodium excreted when acute changes in glomerular filtration are produced by this method.

In 4 patients there was a transient rise in renal blood flow and glomerular filtration while semivertical, suggesting an augmentation of cardiac output by lowering the venous return. However, in the majority of patients pooling of blood in the lower extremities was accompanied by impairment of renal blood flow and sodium excretion.

Relationships of Blood Flow, Oxygen Saturation of Mixed Venous Blood and Blood pH During Extracorporeal Circulation in Man

Emerson A. Moffitt, David E. Donald, Robert T. Patrick, John W. Kirklin, and H. J. C. Swan, Rochester, Minn.

Arterial, central venous and left atrial pressures, arterial and venous blood oxygen saturation, arterial pH, electrocardiogram, electroencephalogram and body temperature have been recorded in 95 patients undergoing open intracardiac surgery.

Controlled gentle vacuum (3 to 8 cm. H_2O) was used to obtain all of the venous return from the patient. Under these conditions blood flow and central venous pressure vary directly with circulating blood volume and have proved a sensitive indicator of the maintenance of this variable in the patient. Blood flows averaging 74 (range: 27 to 220) ml./Kg. of body weight were obtained. Within a given range of blood flow there was an inverse correlation from patient to patient between body weight and venous oxygen saturation. In patients weighing less than 20 Kg., blood flows averaged 90 (range: 45 to 220) ml./Kg./min., and the mean venous oxygen saturation was 73 per cent. In patients weighing 20 to 84 Kg., blood flows averaged 50 (27 to 122) ml./Kg./min. and mean venous oxygen saturation 72 per cent. At these rates of flow the electroencephalogram was maintained normal. The mean arterial pressure was, however, uniformly lower than the preperfusion and postperfusion levels. There were no demonstrable neurologic sequelae.

Analysis of data from moment to moment during perfusion of 46 of these patients demonstrates that changes in blood flow are followed directionally by

changes in venous oxygen saturation as well as arterial and venous pressures. Low or decreasing blood flows were associated with progressive decreases in blood pH, while at higher flows the pH was maintained relatively stable.

It is concluded that adequate homeostasis can be maintained during perfusion at blood flows of approximately 100 ml./Kg. in infants and small children of weights less than 10 Kg. and that a blood flow of approximately 50 ml./Kg. will maintain similar circumstances in adults of weights greater than 40 Kg.

Age and Cardiovascular Fatalities in the Male Farm Population of Indiana, 1949–1955

Wilford H. M. Morris and Robert L. Eichhorn, Lafayette, Ind.

As part of the Purdue Farm Cardiac Project, a study has been made of the age characteristics in the male farm population in Indiana and its association with changes in extent, scale, and type of farming. The average age of the farm operators, 49.6 years, has changed little in the last 20 years.

The male fatalities from 1949–1955 certified from cardiovascular causes have been analyzed. The hypothesis proposed is that farmers, as a group, have a greater average age at fatality from cardiovascular causes than do nonfarmers. This has been demonstrated by the analysis of fatalities for the last 6 years, over 55,000 fatalities in all.

Differences have been noted in the seasonal distribution of fatalities between the farm and nonfarm groups and between different age groups within these 2 occupational groups.

An Evaluation of the Flush Method for Determining Blood Pressures in Infants

Arthur J. Moss, Wallace O. Austin, Wilbert Liebling, and Forrest H. Adams, Los Angeles, Calif.

Blood pressures were measured by the flush method in the upper and lower extremity of 258 normal infants, 1 day to 1 year of age. Comparing 544 readings obtained at the wrist to a like number at the ankle, it was found that the values in the upper extremity were higher in 75.5 per cent of the cases (411 of 544). Measurements in the upper extremity exceeded those in the lower by a maximum of 34 mm. Hg, the average being 5.3. Since the reverse relationship normally exists for the systolic blood pressure, it was felt that the flush method may be a measure of the mean rather than the systolic blood pressure. In support of this, comparative studies in 50 infants showed a close correlation of the "flush" reading to the calculated mean pressure as determined by auscultation. Finally, observations in 10 infants and children comparing the flush method to direct interarterial measurements indicated a correlation which was closer to the mean than to the systolic or diastolic pressure.

The effect of the size of the cuff upon the readings obtained was studied by comparing measurements made with 5 cm., 7.0 cm., and 9.5 cm. cuffs. Values obtained with any of these 3 cuffs were essentially the same.

The accuracy of the method was appraised by comparing readings sequentially determined in the same infants by 2 teams of observers. In 100 infants the degree of correlation obtained indicates that the flush technic is a reliable method for determining the mean blood pressure.

Alcohol in the Therapy of Hyponatremic Edematous States

Herschel V. Murdaugh, Durham, N. C.

The finding of concentrated urines in certain edematous patients with evidence of hemodilution, coupled with the demonstration by previous investigators (Leaf) of antidiuretic activity of the plasma during water loading in dogs with induced hyponatremia, prompted inquiry into the possible role of antidiuretic hormone (A.D.H.) in hyponatremic edematous states. Since alcohol reportedly inhibits the release of A.D.H., it was used in an attempt to induce diuresis. It was found that alcohol could increase urine output during transient postoperative oliguria.

Absolute alcohol (15 to 30 ml. orally in fruit juice or intravenously as a 3 per cent infusion) was then administered to patients with severe postoperative oliguria, water intoxication, postvalvulotomy hyponatremic syndrome, and 1 patient in refractory congestive failure, all of whom had concentrated urines in the face of edema, hyponatremia, and hemodilution evidenced by decreased plasma osmolarity. The response in these subjects was a diuresis with a 3- to 14-fold increase in 24-hour urine output and a return of the plasma osmolarity and sodium concentration to normal. The increases that occurred in plasma osmolarity ranged from 16 to 63 mosm/L., and the increases in serum sodium concentration ranged from 15 to 41 mEq./L. Dilute urines during diuresis, the return of the plasma to a normal sodium concentration in each patient without sodium administration, and electrolyte excretion studies in 2 of the patients indicate that the diuresis obtained was a true water diuresis.

The patient with congestive failure had been refractory to mercurial diuretics and demonstrated a return to responsiveness to mercuhydrin after his plasma electrolytes had returned to normal.

The diuresis in response to alcohol in these patients presents a therapeutic tool in a difficult clinical problem and suggests an altered response in certain hyponatremic states with release of A.D.H. in the presence of a decreased plasma osmolarity.

Presence of an Active Tubular Mechanism for the Control of Urea Excretion by the Kidney of Man and Dog

Hershel V. Murdaugh and Bodil Schmidt-Nielsen,† Durham, N. C.

In the past urea has been considered a substance handled by the nephron without an active mechanism for tubular control of its excretion. Certain features difficult to explain by a passive mechanism for urea excretion coupled with data from the kangaroo rat and the camel have led to further inquiry into urea excretion in man and dog.

Human subjects and trained dogs were studied on a normal diet and following a long period on a low protein diet. In man the urea/inulin clearance ratio dropped from 0.34–0.41 on a normal diet to 0.07–0.13 after 5 weeks of low protein diet. In the dog the urea/inulin clearance ratio decreased from 0.50–0.55 on a normal protein intake to 0.05–0.11 after 2 weeks of low protein intake. These determinations were made during low rates of urine flow with the changes in urea/inulin clearance ratio not accounted for by changes in rate of urine flow or glomerular filtration rate. While on low protein diet the administration of gelatin or urea was followed by a marked increase in the urea/inulin clearance ratio within 3 hours. The glomerular filtration rate and the rate of urine flow were not effected. When the rate of urine flow was higher due to water diuresis the urea/inulin clearance ratio on low protein diet was increased to some extent, but not as high as the ratio obtained on normal diet with a low rate of urine flow.

This study is presented as evidence that a mechanism independent of glomerular filtration rate and rate of urine flow is active in the regulation of urea excretion in the urine of man and dog. It is suggested that this mechanism is similar to the mechanism found in ruminants.

Comparison of the Hypotensive Effects of Reserpine and Rescinnamine

Mahdi Murtadha, New York, N. Y., John J. McDermott, Danbury, Conn., Lucian Fletcher, Jr., Newton, N. J., and J. Marion Bryant, New York, N. Y.

Recent animal studies suggest that rescinnamine may have greater hypotensive effects than reserpine in dogs, while some clinical observations have indicated that it may have a less sedative effect than reserpine. Eighteen hypertensive patients, previously treated with reserpine for 3 to 11 months, were given rescinnamine for a period of 2 weeks to 4 months, following an intermediate period of placebo therapy for 1 to 3 months. The majority had mild asymptomatic essential hypertension.

Rescinnamine was administered in 1 to 5 mg. oral doses daily; reserpine in 1 to 3 mg. doses. Average standing, sitting, and recumbent blood pressures are reported. With rescinnamine, systolic pressure fell 40 to 60 mm. Hg in 1 patient (reserpine 3), 20 to 39 mm. Hg in 3 patients (reserpine 5) and less than 20 mm. Hg in 10 patients (reserpine 6). With rescinnamine, diastolic pressure fell 30 to 38 mm. Hg in 0 patients (reserpine 3), 20 to 29 mm. Hg in 1 patient (reserpine 1), 10 to 19 mm. Hg in 5 patients (reserpine 6) and less than 10 mm. Hg in 8 patients (reserpine 1). The average prerescinnamine blood pressure was 188/115; prereserpine was 186/112. The average fall in pressure with rescinnamine was 9/6 and with reserpine 15/6. The hypotensive effects of both agents are therefore similar, although somewhat less with rescinnamine. Both are of the magnitude to be expected as the result of mild sedation.

There was no essential difference in side effects. Both drugs induced such a degree of nervousness in 1 patient that they had to be discontinued.

Four patients showed slowing of the pulse rate of over 10/min. with rescinnamine (11 with reserpine).

Studies on the Binding of Magnesium, Calcium and Chlorine Ions to Heavy and Light Meromyosin

Luddo B. Nanninga, Bethesda, Md.*

The binding of Mg^{2+} and Cl^- ions to heavy and light meromyosin was studied for different pH and for different free ion concentrations. Between pH 4.5 and 9 the meromyosins are partly precipitated upon addition of $MgCl_2$. After equilibration the mixture is centrifuged. The supernatant and homogenized remainder are analyzed for Mg^{2+} and Cl^- (Mg^{2+} colorimetrically with eriochrome, Cl^- by titration with mercuric nitrate). The Mg^{2+} and Cl^- concentrations are plotted against the protein concentrations for the 2 fractions and the original mixture. A linear relation is found from which bound Mg^{2+} and Cl^- can be calculated. The Mg binding increases from 0 at pH 4.5 to 17 at pH 8 for heavy and to 26 for light meromyosin. Cl is only bound below pH 6 and the binding increases steeply on decreasing pH to 60 at pH 3, as found from dialysis experiments, in which Mg^{2+} and Cl^- were measured on both sides of the membranes. All values are in equivalents per 100,000 Gm. protein and for 10^{-2} free $MgCl_2$.

The maximum number of bound Mg^{2+} (n), the dissociation constants and free energy of binding can be calculated. Values found are for light meromyosin at pH 5.7: pK 2.1, n 15; at pH 7.0: pK 2.63, n 20 and at pH 8.7: pK 2.77, n 30. For heavy meromyosin at pH 5.2: pK 2.0, n 14; at pH 6.0: pK 2.16, n 20 and at pH 7.0: pK 2.59, n 20.

Ca binds in the same way as Mg, which agrees with the superposition of the titration curves in $CaCl_2$ and in $MgCl_2$.

Free Mg^{2+} or Ca^{2+} can be calculated for any myosin—and total Mg^{2+} or Ca^{2+} concentration. At

)H 7 for 10 per cent myosin and 12 10^{-3} M Mg, free Mg is only 10 per cent of total Mg.

In 10^{-2} M $MgCl_2$ heavy meromyosin is negative only above pH 7.5 and light meromyosin only above)H 9.5. Experiments on binding of K^+ showed that 25 equivalents are bound per 100,000 Gm. myosin at pH 7.5 for a free K^+ concentration 0.05 M. K^+ was determined with the flame photometer.

Direct Recording of Pressure Pulses as Displacement, Velocity, and Acceleration

John J. Neal, Jr. and Thomas J. Reeves, Birmingham, Ala.

Analysis of pressure pulses forms 1 of the major cornerstones of our knowledge of circulatory dynamics. Yet analysis is usually limited to measurement of maximal and minimal amplitude, mean amplitude, and to such measurements as can be easily determined where sharp breaks occur in the records. The wealth of information to be found in changes of wave slope and contour is not fully used because accurate analysis of minor slope changes requires tedious mathematic differentiation.

The carotid pressure pulses in 10 normal medical students were recorded directly as displacement, velocity (first derivative), and acceleration (second derivative) using a differential transformer for displacement and a very light linear coil-magnet to sense velocity. Acceleration was recorded after electronic differentiation of the velocity signal. Normal velocity and acceleration patterns were found remarkably uniform.

Times of such events as carotid upstroke, point of maximal pressure rise, start of fast downstroke preceding carotid incisura were more precisely measured from velocity and acceleration tracings than from displacement.

Such events as time and magnitude of acceleration of the pressure rise and maximum velocity of the pressure rise are readily available from such tracings. These constitute a new type of physiologic information and such differentiated pressure pulses could be obtained from any part of the circulatory system.

Inverted carotid acceleratory forces are remarkably similar to simultaneously recorded force ballistocardiograms from an ultra low frequency system.

In aortic stenosis, aortic insufficiency, decreased aortic distensibility, and increased peripheral resistance there are characteristic derivations from the normal pressure pulse.

Velocity and acceleration records of such abnormal pressure pulses tend to exaggerate such derivations and provide data that can be precisely quantitated. Use of such data may possibly facilitate studies as evaluation of ventricular strength and reserve, the genesis of the ballistocardiogram, detection of early valve disease, and other physiologic problems.

Effect of Intracardiac Blood, and of Fluids of Different Conductivities on the Magnitude of Surface Vectors

Clifford V. Nelson,† Portland, Maine, Ramon L. Lange, Salt Lake City, Utah, Hans H. Hecht, Salt Lake City, Utah, Robert P. Carlisle, Salt Lake City, Utah, and Arthur S. Ruby, Salt Lake City, Utah

Blood has a high conductivity and, therefore, may partially short circuit the electric currents generated by the heart as it washes through the cardiac cavities. This effect may decrease voltages measured at the body surface. Quantitative studies were made using an artificial dipole inside dog hearts which were perfused with liquids of different conductivities. After having established the necessary vascular bypasses, a dipole with terminals 2.3 cm. apart was placed in the left ventricular cavity with 1 pole near the apex. In some experiments the dipole was placed within the lateral ventricular wall. The thorax was closed, and the heart was perfused with fluids having resistivities from below 200 ohm cm. (approximately that of blood) to 1000 ohm cm. In other experiments, the heart was excised, and the bypasses established. The preparation was then immersed in a 3-dimensional elliptic cylinder which resembled the human thorax. This was filled with fluid of resistivity 1000 ohm cm. For each perfusate, limb and thorax leads were recorded.

The ratio of deflections produced with high-resistivity fluid to deflections with the lower resistivity-fluid was 1:3, and was uniform over most points of the field. Near the heart, the deflection ratio depended somewhat on the chest points and dipole orientation. When the volume of fluid washing through the heart was increased, the heart dilated and the voltages were further reduced even if resistivity of the perfusate remained unchanged. Accurate plaster models of human lungs inserted on both sides of the heart greatly reduced voltages for lead I, and increased voltages in leads II and III by about 50 per cent.

The magnitude of manifest heart vectors appears to be about 75 per cent of the actual value because of the shunting action of the blood within the heart; it may be less in grossly dilated hearts. The data may offer 1 explanation for "low voltage" deflections of surface electrocardiograms.

Mitral Insufficiency—Treatment by Polar Cross Fusion of the Mitral Annulus

Henry T. Nichols, Philadelphia, Pa.

We have performed a cross fusion of the mitral annulus over the incompetent pole of the mitral valve in 34 cases to date with an operative mortality of 5 patients (14.7 per cent). The technic consists of placing sutures around the mitral annulus so as to approximate the annulus on the septal leaflet side to

the annulus on the mural leaflet side immediately above the incompetent commissure of the valve. By suturing these tendonous-like structures, the septal and mural leaflets are brought into closer proximity so that they can make contact during systole and thus restore competence to the mitral valve.

The immediate restoration of competence to the valve as evidenced to the palpating finger within the heart has been striking and satisfactory in all operated cases. The evaluation of operative results will consist of physical activity, change in systolic murmur, left heart ventriculogram, left atrial pressure and curve contour changes, and changes in heart size.

Effect of Acute Hypopotassemia on Myocardial Potassium and the Electrocardiogram

George C. Nichopoulos and Walter K. Hoffman, Memphis, Tenn.

Fourteen dogs were rendered acutely hypopotassemic using a Skeggs-Leonards hemodialysis unit. Before and after each run, animal weight, NaSCN space, electrocardiograms, plasma Na, K and Cl concentrations, blood pH, blood pressure and hematocrits were measured.

The dialysis was accomplished in approximately 2 hours. Following dialysis, the animals were allowed to stabilize for 90 min. and a final electrocardiographic and blood electrolyte study was accomplished. The animals were then sacrificed and the myocardium analyzed for Na, K and Cl. A control series of 10 animals was subjected to the same procedure with an isotonic dialyzing solution.

Analyses of the data thus obtained revealed the removal of an average 106 per cent of the calculated extracellular potassium from the animals. The electrocardiographic effects of this removal and the consequent depression of serum potassium levels were variable. The most consistent change in the electrocardiogram was that of depression of the S-T segment and depression or inversion of T waves. No significant change in the P-R interval or in the size of P waves could be detected. U waves did not appear. Runs of ventricular tachycardia appeared in 1 animal. All animals exhibited a return of serum potassium levels toward the control value during the 90 min. stabilization period. In 50 per cent of the animals, the S-T and T changes tended to return to control levels; in the remaining 50 per cent, the S-T and T shifts remained the same or increased.

Analysis of heart muscle removed 90 min. after the run, revealed an amazing average K increment of 12 per cent over the control series.

This study would tend to support the theory that the S-T depression and T wave size is a general indication of an alteration in serum potassium levels. It fails to support the findings of Weller and his associates of marked A-V conduction changes in the acute hypopotassemic state. The increment of myocardial potassium present in all animals in the experimental series was completely unexpected, but indicates that the electrocardiographic pattern of hypokalemia does not reflect a state of depletion of intramyocardial potassium.

Biochemical Observations on Human Atheromatosis: Analysis of Aortic Intima

Nancy L. Noble and Robert J. Boucek, Miami, Fla.

The genesis of human atheromatosis may be followed by analysis of normal, early and advanced atheromatous areas of the aortic intima. Aortas obtained from 37 males and 23 females dying without antecedent illness of a protracted nature were stripped of the intima. Intimal tissue was homogenized in saline to separate the saline-soluble ground substance from the insoluble fibrous scleroproteins, collagen and elastin. The report presents results of biochemical analyses of both fractions of these areas of human aortic intima and includes the following determinations: total protein; the amino acids, glycine, proline and hydroxyproline; free and bound hexosamine; cholesterol; total lipids and calcium.

The earliest significant biochemical change observed in atheromatosis is an increase in hydroxyproline in the female tissue. Lipid aberrances occur only after the development of the early lesion and consist of a prominent increase in cholesterol concentration in the advanced atherosclerotic area of both sexes. In the male, the total lipid increase consists only of a rise in cholesterol while in the female, concentrations of other lipids are also significantly greater.

Saline-soluble hexosamine appears to decrease in atheromatosis without a concomitant decrease in the total value, indicating a relative increase in the bound form of this carbohydrate.

No significant increase in the concentration of calcium of the intima occurs with age. There is no significant rise in calcium with atheromatosis in the tissue of the female while a significant elevation with atheromatosis is noted in the male.

Very few differences were noted in the normal tissue of either sex or at any age. The normal intima of the male has a larger concentration of proline and has a significant positive correlation between cholesterol concentration and age when the data are expressed on a wet tissue weight basis ($r = 0.69$, $p < 0.05$). An atheroma found in a young individual does not differ in any of the biochemical constituents studied from an atheroma from an older person. Furthermore, an atheromatous area in a female is not significantly different from a similar area in the male.

Clinical and Hemodynamic Studies of Myocardial Fibrosis

Robert E. Nye, Jr., Frank W. Lovejoy, Jr., and Paul N. Yu, Rochester, N. Y.

Three patients with myocardial fibrosis were studied: 2 proved by autopsy and 1 at operation. Two men and 1 woman, of ages ranging from 33 to 48, had suffered from fatigue, dyspnea, and peripheral edema for periods ranging from 9 months to 3 years. Symptoms began after successful treatment of subacute bacterial endocarditis in 1 case, and without known antecedent in the others.

Clinical examination disclosed generalized cardiac enlargement, accentuation of P_2, apical or precordial systolic murmurs, marked venous engorgement, peripheral edema and hepatomegaly. Two patients had ascites. Only 1 had pulmonary rales. Electrocardiographic abnormalities were nonspecific. None had clinical evidence of rheumatic or arteriosclerotic heart disease.

By venous cardiac catheterization, all were found to have elevated right atrial, pulmonary arterial and pulmonary arterial wedge pressures. Cardiac output was reduced and arteriovenous oxygen difference increased. The right ventricular end-diastolic pressure was elevated but never achieved ⅓ the systolic. The early diastolic dip, well-marked in 2 patients with sinus rhythm and equivocal in 1 patient with atrial fibrillation, always touched the baseline at least during inspiration. The atrial pressure contours exhibited typical or suggestive M or W shaped complexes, with little or no respiratory variation in mean pressure.

The similarity of these findings and of their probable mechanism to those of constrictive pericarditis has been noted by others. In our experience, the difference is one of degree. Patients with myocardial fibrosis have lower atrial mean pressures than patients comparably disabled by constrictive pericarditis; the right ventricular early diastolic dip is more likely to touch or go below the baseline, and the end-diastolic pressure less likely to achieve ⅓ the systolic. There is some overlapping between the 2 groups, however, in some of these respects.

Histologically, myocardium of 2 fatal cases was replaced to an unusual degree by fibrous tissue.

Long-Term Anticoagulant Therapy: Its Practice and Problems

John H. Olwin and Oglesby Paul, Chicago, Ill.

The authors have reviewed a group of 70 patients who have received long-term (up to 9 years) anticoagulant therapy at the Presbyterian Hospital, Chicago. All patients received an oral anticoagulant for a minimum of 6 months uninterrupted treatment and during therapy had average prothrombin levels (as determined by the 2 stage method) below 30 per cent.

The series includes 40 males and 30 females. Indications for treatment included acute and recurrent thrombophlebitis (18 cases), retinal vein occlusion (14 cases), arterial embolism from the heart (10 cases), peripheral arteriosclerosis (5 cases) and other thrombotic conditions (5 cases). Fifty of the patients have been treated for over a year, and 21 for more than 3 years. Drugs employed included Dicumarol (19 cases), Hedulin (10 cases), Dipaxin (9 cases), Tromexan (5 cases), Sintrom (1 case), and combinations of these (27 cases).

Seven patients were true therapeutic failures in that further thrombotic lesions appeared while under apparent satisfactory control (4 new myocardial infarcts, 1 probable peripheral embolism, 1 recurrent thrombophlebitis, 1 retinal vein occlusion) and 2 of these died. Five patients experienced new thromboses, 3 with emboli, due to technical failure on the basis of inadequate depression of prothrombin levels. Eleven complications due to bleeding were encountered, 9 of which were not serious and were readily controlled; 2 were serious (cerebral hemorrhage definitely in 1, probable in another) and led to death. Uterine bleeding during anticoagulant therapy twice revealed the presence of hidden malignancy.

Factors affecting the success of treatment will be reviewed including the action of other agents (alcohol, salicylates, xanthines), and the need for individualizing the handling of each case.

The authors believe long-term anticoagulant therapy can be safely employed for the conditions cited and their method of following such cases will be described.

Use of an Oral Digoxin in Infants and Children with Congestive Heart Failure: A Clinical Study

Patrick A. Ongley and Alexander S. Nadas, Boston, Mass.

Fifty patients with congestive failure and suffering from various forms of congenital heart disease, both cyanotic and acyanotic, constitute the material for this study.

Adequate digitalization was assumed to have occurred when there was either satisfactory clinical response in the signs of congestive heart failure, or definite signs of digitalis toxicity on the electrocardiogram.

The Digoxin dosage was calculated individually for each patient and was based on age and weight. For the purposes of this paper our patients have been divided into 2 groups 0–2 years, and 2–10 years.

Digitalization of each patient was carried out with careful clinical and electrocardiographic examination before each dose of Digoxin. Dosage schedule was

simple, consisting of 0.01 mg./lb. of body weight and repeated at 6 hourly intervals until adequate digitalization occurred.

The dosage for adequate digitalization of the patients from 0–2 years was 0.03 to 0.04 mg./lb. of body weight and for the group age 2–10 years 0.02 to 0.03 mg./lb. of body weight. In both groups the maintenance dosage was found to be ¼ to ⅓ of the original digitalizing dose.

Digitalis toxicity was revealed by various forms of heart block, nodal rhythm, or atrial ectopic beats when high dosage was used. Gastrointestinal symptoms and ventricular ectopic beats were rare.

The drug is considered to be useful in any case of congestive failure, and especially so in those cases requiring either rapid digitalization or rapid digitalis excretion.

Clinical Use of a New Hand-Controlled Positive-Negative Phase Respirator During Thoracic Surgery

John J. Osborn, Philip J. Bailey, Frank Gerbode, and Thomas Edgington, San Francisco, Calif.

Inadequate pulmonary ventilation is a serious hazard to the patient undergoing thoracic surgery. Yet vigorous positive-pressure artificial respiration may interfere with the circulation of the blood. There is now considerable evidence that a negative pressure phase (withdrawal of expired air under mild negative pressure) will increase the effective ventilation with little disturbance of the circulation.

Various mechanical pump-respirators have been designed to offer alternating positive and negative pressures, but a completely mechanical unit loses much of the flexibility and direct contact with the patient which the anesthetist enjoys with direct positive pressure respiration by hand-pressure on the anesthetic bag.

We have described elsewhere a new respiratory unit for the operating room. In use, the anesthetist "breathes" the patient in the usual way by hand-pressure on the bag. During expiration, the unit automatically supplies negative pressure for a variable amount of time. This apparatus thus maintains the close connection between anesthetist and patient, but adds the advantage of a negative phase during expiration.

We will present evidence that with this apparatus pulmonary respiratory minute-volume can be much increased without increase of mean intrapulmonary pressure. Concurrently alveolar pCO_2 may be reduced. Clinical examples will be presented of the use of this apparatus during thoracotomy and particularly during cardiac surgery. Comparison will be made of positive-negative respiration and of ordinary positive-pressure respiration for their effect on the patient as shown by changes in alveolar pCO_2, blood pH and various indices of effectiveness of the circulation.

Studies of the Mechanism of Pulmonary Infarction

Brent M. Parker and John R. Smith, St. Louis, Mo.

The precise mechanism of the production of pulmonary infarction is not clear. It has been assumed that the bronchial arterial system functions as a collateral circulation when pulmonary arterial flow is obstructed by an embolus, and that failure of the bronchial collateral stream permits the development of infarcts. This assumption has recently been challenged. The problem of pulmonary embolism and the genesis of infarction has been restudied in this laboratory.

Pulmonary infarction in dogs was regularly produced by the establishment of femoral arteriovenous fistulas, followed by embolism of 1 or 2 lobar arteries with foreign bodies introduced through the external jugular veins. The bronchial arterial collateral blood flow was measured in animals with and without infarcts, using the method of Williams and Towbin; changes in the vascular anatomy of the lungs were likewise observed by corrosion methods.

The evidence indicates that a large pulmonary embolus in the normal dog induces bronchial arterial expansion distal to the embolus, so that the alveolar circulation becomes largely supplied by the bronchial arterial stream; infarction does not occur. Animals with A-V fistulae, with lung infarcts from emboli, also developed expanded bronchial arterial vessels in the affected lobe(s). Measurement of bronchial flow indicated that there was no significant difference in the degree of collateral circulation in embolized animals with and without infarction. It is evident that mechanisms other than the extent of the bronchial circulation are concerned in infarct formation following pulmonary obstruction in animals with peripheral fistulae. It is possible that under the conditions of lung infarction produced in this way, the fistulas induce hemodynamic changes which prevent the adequate function of the expanded bronchial arterial system.

Nonpenetrating Traumatic Injury to the Aorta

Loren F. Parmley, Jr., Thomas W. Mattingly, William C. Manion, and Edward J. Jahnke, Jr., Washington, D. C.

Review of 157 cases of traumatic rupture of the aorta available at the Armed Forces Institute of Pathology, or studied at Walter Reed Army Hospital, revealed data of clinical importance. The 5 types of force acting to produce these injuries vary, most commonly being encountered in automobile accidents. One hundred thirty-nine of these cases of aortic rupture were immediately fatal. Eighteen patients survived for variable periods, from a few hours to many months, before termination by death or adequate diagnosis and treatment intervened.

Of importance is that 11.4 per cent survived aortic rupture, 5 cases being complete transections, for a sufficient period to allow diagnosis and treatment. Analysis of the sites of rupture revealed the greatest number, 56 or 36.3 per cent, occurred at the isthmus. Being the junction of relatively fixed and mobile segments of the aorta, it is subject to greatest strain in the event of nonpenetrating trauma.

The next most frequent site of rupture was the ascending aorta where 31 or 19.7 per cent occurred. However, these ruptures were usually associated with extensive cardiac and/or other injury, with very few survivals. Of clinical significance was the revelation that 52, or 33.1 per cent of the patients incurring traumatic aortic rupture presented minimal or no obvious external evidence of chest injury. A definite correlation with vertebral fracture and site of rupture was established in this series.

Three representative cases of this group are discussed to present the clinical and pathologic features of traumatic aortic rupture. It is emphasized that any accident case where there is chest injury or dorsolumbar vertebral fracture, the possibility of aortic rupture should be entertained, but that a lack of external evidence of chest injury does not exclude the possibility of aortic rupture.

Congenital Complete Atrioventricular Block: A Hemodynamic and Clinical Study

Milton H. Paul, Abraham M. Rudolph, Patrick A. Ongley, and Alexander S. Nadas, Boston, Mass.*

Cardiac catheterization has been performed in a group of 6 patients (age 8 months to 14 years) with congenital complete atrioventricular block. This group was clinically homogeneous in that all had significant lower left sternal border systolic murmurs, distinct low frequency diastolic murmurs, and slight to moderate cardiomegaly.

Cardiac catheterization revealed an atrial septal defect in 2 patients; however, no left-to-right shunt was demonstrated in the other 4 patients. In these 4 patients right atrial mean pressures were normal, right ventricular systolic pressures were slightly elevated and in 1 patient a small gradient was demonstrated across the pulmonary valve. The tricuspid and pulmonary valves, with this 1 exception, appeared hemodynamically normal. Pulmonary wedge pressure was moderately elevated in only 1 patient. Calculated stroke volumes in the 4 patients without demonstrable cardiac shunts were markedly elevated (66, 41, 96, and 107 ml./M.^{2}/stroke).

This group of patients presents some of the auscultatory findings commonly attributed to a valvular lesion or an intracardiac shunt. These patients were indeed classified as having significant congenital heart disease with large left-to-right shunts prior to physiologic study.

The systolic murmur and cardiomegaly are discussed in terms of the possible role of a high stroke volume flowing through relatively normal cardiac valve orifices. The diastolic murmur is possibly related to the occurrence of a high diastolic flow through the atrioventricular valve, accelerated by recurring atrial systole.

Evaluation of Q aVf by the Initial Sagittal QRS Vectors

Morton L. Pearce and Myron G. Chapman, Los Angeles, Calif.

The electrocardiographic diagnosis of posterior myocardial infarction (PMI) is often difficult. When healed the electrocardiographic residuals may be no more than tiny Q waves in leads III and aVf. On the other hand, occasional records are seen with prominent Q waves in leads III and aVf, but with no evidence of posterior infarction at autopsy. For example, 20 out of 25 autopsied cases with PMI had either a Q aVf > 25 per cent R aVf or Q aVf > .04″ while 10 out of 45 cases without PMI had a Q aVf > 25 per cent R aVf and 2 out of 45 had a Q aVf > .04″.

For these reasons, and because of the experience of Milnor (Bull. Johns Hopkins Hospital **89:** 281, 1951), we have recorded simultaneously leads aVf and the Wilson back lead at 75 mm./sec. in all cases showing a Q wave in aVf on the standard electrocardiograph. This report concerns the 70 autopsied cases mentioned above, 25 with PMI and 45 without PMI.

Sagittal vectors at .01″ and .02″ were constructed and their direction determined. Standardization was 1 mv. 1 cm. for both leads. The horizontal and anterior direction was 0° and the headward direction was 90°. It was decided, after inspecting the data, to classify all records with a .02″ vector of 65°–150° as positive and all others as negative. Employing these criteria the following results were obtained.

In 25 cases with PMI.: 14 had a Q aVf > .04″ and a positive .02″ vector (+V) 10 had a Q aVf < .04″ and a +V, 1 had a Q aVf < .04″ and a negative .02″ vector (−V).

In 45 cases without PMI.: 2 had a Q aVf > .04″ and a −V, 36 had a Q aVf < .04″ and a −V, 7 had a Q aVf < .04″ and a +V.

It can be seen that a negative .02″ sagittal vector is highly accurate in excluding a PMI. in the presence of a Q aVf, and a positive .02″ vector in the presence of a Q aVf > .04″ is pathognomonic of a PMI.

Distribution of Renin in the Rabbit Kidney

W. Stanley Peart, London, England, David B. Gordon, Los Angeles, Calif., William F. Cook, London, England, and George W. Pickering, London, England.*

A technic for the assay of very small amounts of renin by measurement of its effect on the blood pressure of the anesthetized rat has been developed

by one of us (W. S. P.). By this method renin can be determined in as little as 5 mg. (dry weight) of rabbit kidney tissue.

We have assayed the renin content of the rabbit kidney in successive layers, each about 0.2 mm. thick, from the outer surface of the cortex down into the medulla. Our results indicate that there is little or no renin in the outermost layer of the cortex, which layer contains tubular tissue but no glomeruli. The next layers, which do contain numerous glomeruli, have a high renin content; the highest, in fact, of any part of the cortex. In the next deeper layers, the renin content diminishes and so does the glomerular count. Progressively, as one approaches the medulla, the renin content of the cortical tissue decreases, but it is important to note that the decrease in assayable renin content is proportionately much greater than the diminution in the number of glomeruli. Upon reaching the medulla, the renin content falls to 0.

Although there is a striking association between the presence or absence of glomeruli and the presence or absence of renin, there is, at the same time, a dissociation between the number of glomeruli in different layers of the cortex and the amount of renin assayable therein. The data suggest either that the renin is in some tissue closely associated with glomeruli, or that it is actually present in the glomeruli but not in equal amounts in all glomeruli.

Selective Hyperlipoproteinemia Alteration Through High Potency B-Complex and C-Vitamin Administration

Robert M. Perlman, San Francisco, Calif.

Extraordinarily heavy, high potency B-complex and ascorbic acid therapy was administered to a relatively large group of adult male and female humans. Serum lipoprotein assays, according to technic and method of Gofman, were performed pre, during and post-therapeutically. Responses to vitamin agent, placebo and discontinuation of therapy were noted. Significant quantitative selective lowering of larger-sized S_f molecular categories occurred as the result of such vitamin treatment.

In doses employed, the combination of vitamins effected dramatic transitions, causing break-down of larger serum lipoprotein groups (S_f 12–400 and, especially, S_f 20–100 and 100–400) into smaller-sized classes (S_f 0–12, S_f 12–20). Shifts of this nature were much more frequent than remarkable changes in total serum lipoprotein titres, usually paralleling subjective and objective patient improvement as judged by general, clinical and laboratory data.

Placebo substitution caused rapid regression of therapeutic gains. Renewed improvement(s) occurred with restoration of basic vitamin therapy.

The atherogenic index (Gofman's A.I.), or alterations of same, seemed insignificant, relatively, in diagnosis, evaluation, and/or prognosis of atherosclerosis and/or coronary heart disease or syndromes, in most cases studied here.

Mechanism(s) of therapeutic action(s) remain unfathomed. Augmentation of nonspecific, adrenal glandular anti-stress, response-potential, together with other specific and nonspecific defense factors involving liver, kidneys, and endocrine glandular chain are postulated intermediaries en route to the above-noted, accomplished end-results of this study.

Whether or not the aforementioned positive results are accomplished via individual(s), diverse group(s) or the composite of component ingredients contained in the vitamin preparation used in this study is unknown. Vast significance, however, has been attributed generally to the probable etiologic culpability of disturbed lipid and/or serum lipoprotein metabolism in atherogenesis and coronary heart disease; consequently, wide-spread interest has been engendered in an intensive search for possible *lipotropilysins*. One probable effective agent in the latter category forms the nucleus of the present study.

Some New Developments in Fundamental Hemodynamics

Lysle H. Peterson,† Philadelphia, Pa.

The magnitude of systolic and diastolic pressure is commonly considered to be a most significant clinical sign of cardiovascular function. Pulse pressure may be 100 per cent higher in peripheral vessels then it is in the central aorta. A popular explanation is that the distortion is due to fusion of incident waves, and waves which are reflected from the "periphery" of the arterial system. This hypothesis is embodied in the view that the arterial system is a resonating compression chamber. An extreme extension of this view is that a "standing" wave is produced. There are, however, many theoretic and experimental objections to the reflected wave concept. Between the aortic root and the capillaries, the system undergoes vast, complex, asymmetrical branching. The area of the system increases, tending, theoretically, to cause negative pressure reflection. Contrariwise, the vessels tend to become stiffer toward the periphery, tending, theoretically, to produce positive reflections. Moreover, these 2 opposing reflection factors are progressively distributed; thus, their possible effectiveness would be diffused. Further, if there were reflected waves, they would have to retraverse the same diffused, opposing conditions. Experimentally, specifically shaped pressure pulses, induced within the aortae of living, intact dogs were transmitted without evidence of distortion due to reflected waves. Further, pressure waves, induced within peripheral arteries, underwent marked, progressive attenuation during their retrograde transmission. In addition to demonstrating the inadequacies of the

reflected wave hypothesis, these data show that the arterial system is highly damped. The types of distortion which are observed, therefore, can be explained on the basis of harmonic dispersion and attenuation, since theory and experiment have shown that, in systems possessing boundary damping, wave velocity and attenuation is frequency dependent. These experiments also demonstrate that the magnitude of central arterial pulse pressure is dependent upon important parameters other than volume change and vessel distensibility. Another consideration of this work suggests that the arterioles constitute only a small proportion of total "peripheral resistance."

An Enforced Mass-Culture Program for Control of Primary Attacks of Rheumatic Fever: Report of One Year's Results

Brendan P. Phibbs, Rodney C. Lowe, and Donald Becker, Casper, Wy.

During the school year 1955–56, a compulsory mass-culture streptococcal detection and control program has been applied in the Casper School System (5,846 children). The goal has been the prevention of primary attacks of rheumatic fever. The program was organized in 7 steps: 1. Rheumatic fever control committee formed in County Medical Society. Physicians assigned to each school as instructors and supervisors. 2. Teachers and principals instructed in significance and general characteristics of streptococcal infections. 3. Volunteer workers from PTA and service groups trained in recognition of streptococcal infections and in technics of throat-swabbing (10 workers per school). Criteria employed: (a) beefy redness of throat or tonsils, (b) purulent exudate on throat or tonsils, (c) acute cervical adenopathy, (d) fever. 4. At a prearranged time each morning any child manifesting or describing symptoms of upper respiratory infection is examined by volunteers; suspicious children have throats swabbed and cultured on blood-agar. Positive reports phoned to school within 24 hours. 5. Children found infected are sent home with a form letter directing parents to take the child to the family doctor for antibiotic therapy. 6. Infected children are excluded from school until adequate therapy is initiated. Form letters are initialed by the medical doctor. Free penicillin furnished for hardship cases. 7. Recheck cultures performed after 10 days on infected children.

Results. Total cultures taken, 8,120. Total positive for hemolytic strep, 587 (7.2 per cent). Small schools with stable populations, total positive cultures fell from 10–15 per mo. to 0–3 per mo. during the school year. Larger schools with transient populations; monthly totals fluctuated irregularly. Indices of infection calculated for each school as positive cultures per student-day (×1000). Indices varied with economic level and sanitation. Two schools including poorest segments of population gave indices of 2.3 and 4.1. All other schools ranged from .4 to .8. High incidence in the 2 above mentioned schools proved due to reinfection from families with abysmal living standards and no idea of significance of purulent respiratory infections. School with index of 2.3 gave an overall incidence of 18 per cent positive cultures. Many positive cultures were obtained from throats not clinically typical. Repeated swabs sometimes were necessary to detect the organism; positive cultures often obtained on third or fourth day of successive swabbing. One city-wide epidemic appeared in March with abrupt rises in widely separated schools.

Three known cases of rheumatic fever occurred in the entire group, all occurred in children who had deliberately evaded throat swabbing or who had been out of town at the time of infection.

Cost of program. $500.

Conclusions. Mass-culture methods for prophylaxis of primary attacks of rheumatic fever are simple and effective. Detection of carriers and enforced treatment of all streptococcal infections appears to abort epidemics and diminish total incidence of infection. Training of volunteer workers disseminates accurate information throughout the community. Actual incidence of rheumatic fever in such a group is greatly below that expected from the number of positive cultures (3 as against expected 18). Epidemiologic data gathered indicate that the hemolytic streptococcus concentrates in poor economic areas, where ignorance and lack of sanitation are the predisposing factors. The organism is present in endemic form in upper-respiratory foci with occasional epidemic eruptions. Blood-agar plating is about 90 per cent accurate, roughly 10 per cent of "positives" are group D enterococci on subculture.

Effects of Dietary and Hormonal Imbalance on Coronary Atherogenesis in Cholesterol-Fed Cockerels

Ruth Pick, Jeremiah Stamler,† and Louis N. Katz, Chicago, Ill.

Based on previously accumulated epidemiologic, clinical and experimental findings, the present studies were undertaken to explore further the interrelated roles of dietary and hormonal factors in atherogenesis.

The first group of experiments was designed to investigate the influence of dietary imbalances on atherogenesis in cholesterol-fed cockerels. These animals were fed synthetic diets in order to control intake of several dietary constituents. The results suggest that the atherogenic effect of a cholesterol-supplemented diet is influenced by the level of amino acid and protein intake. Imbalance between high cholesterol-lipid and low methionine ingestion

appeared to be particularly atherogenic, whereas protein supplementation may be protective.

The second set of experiments explored the possible influence of exogenous insulin on the enhanced susceptibility of the diabetic to atherosclerotic vascular disease, particularly the loss of the usual premenopausal female resistance to coronary atherosclerosis. The results of these experiments showed that exogenous insulin given to normal nondiabetic chicks on an atherogenic diet had the following effects: (1) it enhanced aortic and coronary atherosclerosis; (2) it prevented the regression of lesions usually occurring after cessation of cholesterol feeding; (3) it counteracted the protective effect of estrogens on coronary atherogenesis; (4) when given in combination with adrenal hormones (adrenaline or hydrocortisone), it induced particularly severe coronary atherosclerosis. These observations pose basic problems concerning exogenous insulin as a possible atherogenic factor in diabetic patients.

These experiments stress the complexity and multiplicity of factors, acting alone or in combination throughout the life span, to retard or enhance atherogenesis in the individual.

Electrocardiographic Diagnosis of Ventricular Tachycardia

Sheldon T. Pinsky and Charles Fisch, Indianapolis, Ind.

An accurate diagnosis of ventricular tachycardia is a prerequisite for intelligent management of this disorder, evaluation of various therapeutic agents, and study of the natural course of the disease.

Accepted electrocardiographic criteria for diagnosis of ventricular tachycardia include regular or slightly irregular rapid ventricular rate, prolonged QRS complex, and the demonstration of an independent sinus rhythm. However, 2 or sometimes even all 3 of these criteria may be found in certain of the supraventricular arrhythmias, thus leading to an erroneous diagnosis. Paroxysmal atrial tachycardia, atrial fibrillation, atrial flutter, and A-V dissociation, when complicated by aberrant conduction or pre-existing bundle-branch block, may mimic ventricular tachycardia. Occasionally, Wolff-Parkinson-White syndrome with atrial fibrillation can be confused with ventricular tachycardia.

Electrocardiograms are presented illustrating complex supraventricular arrhythmias that resemble ventricular tachycardia, and differential diagnosis is discussed. Unequivocal diagnostic criteria were emphasized by Langendorf and include the presence of fusion (combination) beats and "captures." These serve to demonstrate the presence of 2 independent pacemakers.

Mechanism of Production of Ventricular Fibrillation Following Hypercapnia

Ananda S. Prasad, Ernest B. Brown, Jr., and Edmund B. Flink, Minneapolis, Minn.

Sudden return to breathing air following 2 to 4 hours of breathing a high CO_2 mixture produces cardiac arrhythmias in dogs and even ventricular fibrillation and death. Serum potassium rises during hypercapnia and the first 5 min. of the recovery phase. As recently reported by Brown, the elevation of plasma potassium in these circumstances is not sufficient of itself to produce the severe cardiac effects. Experiments to determine also the changes in ultrafiltrable calcium during respiratory acidosis will be described.

Mongrel dogs anesthetized with thiopental sodium were used. In 1 group of dogs, femoral artery blood samples were collected under oil before, during and following breathing 30 per cent CO_2 for 30 min. A centrifuge was used for ultrafiltration. During respiratory acidosis the ultrafiltrable calcium increased slightly, but during recovery period it decreased markedly below the original level, while the total calcium and proteins remained essentially unchanged.

In another group of dogs, 30 per cent CO_2 mixture was used for 2 hours followed by 40 per cent CO_2 for another 2 hours. Blood pressure and electrocardiogram were recorded simultaneously. Serum potassium, phosphorous, total and ultrafiltrable calcium were determined in each sample. The ultrafiltrable calcium after 30 min. of CO_2 breathing increased slightly, but at the end of 4 hours, and again after 5 min., of breathing of air decreased sharply concomitantly with hyperkalemia and hyperphosphatemia. Recent experiments by Braun and associates show that hypocalcemia causes an increased susceptibility to potassium toxicity.

In conclusion, the ventricular fibrillation following hypercapnia is apparently due to potassium intoxication in the presence of decreased ultrafiltrable calcium.

Types of Aortic and Arteriographs which are Effective Experimentally and Clinically

Gerald H. Pratt and Arthur A. Levine, New York, N. Y.

Since 1951, an active research and clinical program on the use of various substitutes for the aorta and the arteries has been carried on. The autogenous vein grafts previous to 1951 have been analyzed. The use of autogenous arteries, autogenous skin and autogenous bowel with and without its mesentery have been used to replace the aortas in dogs. Results of this work is reported for the first time.

Various types of prosthetics have been utilized, both in the experimental animal and on clinical

patients. These are: Dacron, Nylon of the Chemstrand type, Nylon of a seamless type, Ivalon (polyvinal) and closely woven steel mesh cloth. The Nylon types have also been used on human patients.

The results of this work, both experimentally and clinically, is presented. Pre- and postoperative aortograms will detail the functioning of these grafts and an effort will be made to demonstrate the value of them, both in areas where there is very little flexion and in areas such as in the adductor canal where there will be considerable movement and stress and strain on the graft.

This is a 4-year work and was supported, in part, by a grant from the United States Navy. As part of this work, aortograms and arteriograms showing normal and abnormal collateral circulation as it develops with occlusion, is demonstrated.

While innumerable articles on the use of grafts are presented at various meetings, it is felt that this report on multiple types of replacements for diseased vessels is timely and will be of value.

It is our belief, based on clinical experience and pathologic examination of the grafts in the sacrificed animals, that homografts are the best available for any grafting where there will be considerable flexion or contraction of the part, but that prosthetic grafts, particularly of the Nylon type, or Ivalon, make excellent substitutes and can be used clinically. Their use is particularly indicated in trauma to young individuals where sections of arteries are lost. Even in grafts which later occluded, collateral circulation was found to be extremely well developed. This was particularly demonstrated in one 17-year-old individual whose vein graft occluded 4 years after its insertion.

Studies on Dyspnea and Pulmonary Edema in Patients with Rheumatic Heart Disease While Breathing High Oxygen Mixtures

Oldrich C. Prec, Ormand C. Julian, and Frederick Wood, Jr., Chicago, Ill.

Oxygen debt and ventilatory cost of moderate exercise was studied in 26 patients with RHD before mitral commissurotomy and restudied in various intervals up to 2 years after surgery. In majority of patients the hemodynamic data obtained by cardiac catheterization are available. The results indicate that (a) the total excess of ventilation resulting from exercise is 60–230 per cent higher than in the control group, (b) the oxygen debt is increased up to 600 per cent, and (c) that the increase in oxygen debt is predominantly due to lactic acid fraction. The repayment of the oxygen debt only exceptionally followed the exponential pattern found in controls.

In order to elucidate the possible mechanisms of the increased respiratory cost of exercise (1) studies of distribution pattern of the alveolar air were done in a selected group of 12 patients with pulmonary capillary pressure above 20 mm. Hg and (2) the respiratory response to CO_2 inhalation was carried out in 12 patients. Nitrogen clearance technic was used for the distribution studies. Eight patients showed normal distribution with the mean effective coefficient of ventilation K = 1.02 associated with the mean minute ventilation of 5.47 L./M.^{2} Four had grossly abnormal distribution patterns with an increase in the functional residual capacity in 3 of them. It is concluded from these studies that there is no evidence of increased bronchomotor tone as postulated by some investigators.

Inhalation of 5 per cent CO_2 caused increase in minute ventilation from 160 to 240 per cent of the control value. The blood analyses carried out simultaneously were as follows: pCO_2: 37 mm. Hg with air, 43 mm. with CO_2; pO_2 85 mm. with air and 102 mm. with CO_2; pH 7.38 with air and 7.33 with CO_2. These results do not differ significantly from those obtained in normal controls.

Blood studies in chronic pulmonary edema so far indicate that there is marked retention of CO_2 and marked decrease of pO_2 but the pH remains within normal limits. Work on this part of the problem continues.

Lactic acid formation, patterns of its removal after exercise and its effect upon respiration are being investigated.

Personality, Emotional and Neurologic Changes Associated with Heart Disease and Cardiac Surgery

Walter S. Priest, Misha S. Zaks, George K. Yacorzynski, and Benjamin Boshes, Chicago, Ill.

Patients undergoing mitral commissurotomy were observed to show a higher incidence of acute postoperative psychoses and suicide than patients undergoing other major surgical procedures. Sixty patients with acquired and congenital cardiac lesions have been studied. Cardiac catheterization was performed on all patients with congenital and chronic rheumatic lesions to serve as a basis for objective evaluation of improvement in cardiac dynamics resulting from surgery. Neurologic examination, psychiatric interview, and psychologic testing were performed on all patients before operation and 2 to 3 weeks postoperative. Retesting was done 6 months, 1 year, and 2 years postoperatively. Recatheterization was done at 1 year. Of the 60 patients, 47 had rheumatic valvular deformities: 38 mitral stenosis, 23 operated on, 15 not operated, 3 examined postoperatively only. Six aortic lesions. Of the 13 nonrheumatic lesions, 9 were congenital, 4 coronary artery disease. Comparable groups of individuals without heart disease were studied as

controls. These include persons with and without psychiatric disorders.

It was found that cardiac patients as a whole can be differentiated from normal controls by a higher score on depression, suicidal trends, rigidity, attitudes toward sex, anomie and aggressive feelings. Patients with mitral stenosis consistently show higher performance than verbal I.Q. and signs of cortical organicity. The incidence of transitory signs of organic brain involvement postoperatively was higher than previously reported. Psychologic disturbances persisted for 6 to 8 months after surgery and had a significant effect on rehabilitation.

Excessive Pressor Response to Infused Catecholamines as a Clinical Pretoxemia Test

Wilhelm Raab, Gerhard Schroeder, Richard Wagner, and Wilda Gigee, Burlington, Vt.

The pressor responses to infused norepinephrine and epinephrine are augmented by pretreatment with desoxycorticosterone acetate (Raab, 1942; Raab and associates, 1950; Sarre, 1944; Vanatta, 1955), presumably due to the DCA-induced alteration of the intra-extracellular cationic gradient and its influence on the electric membrane potential of the contractile cells. This phenomenon, and the behavior of the salivary Na/K ratio (Frawley and Thorn, 1951) were used as criteria of mineralocorticoid activity in 60 nulliparous controls, 100 cases of uncomplicated pregnancy and 63 abnormal pregnancy cases, all between the twenty-eighth and thirty-fourth week. Average blood pressure deviations during standardized intravenous catecholamine infusions were recorded. There was no difference between the controls and the normal pregnancies. In 24 cases with albuminuria and in 50 with edema (overlapping groups) the average pressor responses were significantly increased. The greatest increases occurred in 17 normotensive pregnant women who became hypertensive subsequently. All of the 10 maximal hyper-reactors (4 entirely asymptomatic; 3 only edematous) developed toxemia after the test; 3 became eclamptic. The average salivary Na/K ratio diminished from a control average of 0.70 in the following order: normal pregnancies (0.52); edema group (0.43); albuminuria group (0.38); prehypertensive group (0.30), suggesting mineralocorticoid overactivity. An average systolic pressure rise of 60 mm. or more during infusion of norepinephrine (0.3 gamma/Kg./min.; 5 min.) suffices to indicate impending toxemia.

Observations on Acute Pulmonary Congestion with Mitral Stenosis

Bertha Rader, New York, N. Y.

Nine women with mitral stenosis have been observed during episodes of acute respiratory distress with symptoms of cough, fever, dyspnea, and frequently hemoptysis. One of these women had 3 attacks of this kind, twice in the eighth month of pregnancy at a year's interval. All 3 attacks were preceded by upper respiratory infections. One patient had the illness twice, once in the first trimester of pregnancy, but preceded on both occasions by an upper respiratory infection. A third patient had 1 attack during active rheumatic carditis. All 3 patients showed hilar shadows or density over part of a lobe of the lung. The bacteriologic studies of the sputum were negative. In all, the diagnosis of pneumonia was made and in all the x-ray abnormalities disappeared in 3 to 5 days.

Hemodynamic studies on 2 of these patients showed elevated right heart and pulmonary wedge pressures and 1 of them underwent mitral commissurotomy. The third patient had normal hemodynamics in the right heart.

A fourth patient in the second trimester of pregnancy died during such an attack within 24 hours of admission. Necropsy revealed a heart of normal size with a mitral valve of pin-point diameter.

Three of these patients received digitalis without clinical response.

The remaining 5 patients showed a similar clinical syndrome but of lesser severity. Three of these women were pregnant. Only 1 of this group had cardiac catheterization, and the measurements were within normal limits.

This group of patients shows the pulmonary congestion which complicates obstructive mitral stenosis. When some factor like infection, or pregnancy, or both, raises the pressure in the pulmonary artery the "pinch-cock" effect of the mitral valve produces pulmonary edema. The diagnosis of bronchopneumonia, or rheumatic pneumonia is often made.

The clinical picture in all is so uniform as to suggest its being an integral part of mitral stenosis.

Pulmonary Blood Volume in Mitral Stenosis

Elliot Rapaport, Albany, N. Y., Hiroshi Kuida, Boston, Mass., Florence W. Haynes, Boston, Mass., and Lewis Dexter, Boston, Mass.*

The Stewart-Hamilton and Bradley methods for "pulmonary" blood volume determination were simultaneously studied 19 times during right heart catheterization in 16 patients with mitral stenosis utilizing chromium^{51} tagged red cells and T-1824.

No evidence of a systematic error in cardiac output was discerned between the indicator dilution and Fick methods. The ratios of cardiac outputs using Evans Blue dye to those determined with chromium^{51} red cells averaged 1.00 (s.d. = .05). This suggests dye in significant amounts does not leak out of the pulmonary bed during its initial circulation despite high "pulmonary capillary" pressures.

"Pulmonary" volumes ranged from 595 to

1111 ml./M.² (23.2 to 40.1 per cent total blood volume) by the Stewart-Hamilton and 423 to 1206 ml./M.² (17.1 per cent to 42.7 per cent total blood volume) by the Bradley method. No significant correlation was detected between pulmonary blood volume and cardiomegaly, secondary pulmonary vascular disease, mitral valve area, or "pulmonary capillary" pressure. A significant correlation was demonstrated between cardiac output and pulmonary blood volume ($r = +.75$). It would appear that pulmonary blood volumes in mitral stenosis, although generally in the normal range, are elevated in respect to the low cardiac outputs.

A good correlation was seen between individual volumes calculated by the Bradley arteriovenous equilibration method and the traditional Stewart-Hamilton method ($r = +.82$, $p < .01$). Results indicate that with careful analytic technic the Bradley method can be satisfactorily applied to measurement of "pulmonary" blood volume.

Average mean transit time was shorter for cells than for dye in all patients (mean ratio .95, s.d. = .03). This resulted in a lower "pulmonary" compared to large vessel hematocrit by the Stewart-Hamilton technic. Mean "pulmonary" to large vessel hematocrit ratio by the Bradley method was .91 ($p < .01$). Since both methods measure predominately large vessel compared to actual capillary blood, the hematocrit of the pulmonary capillary bed itself must be considerably less.

Surgical and Diagnostic Problem of Cardiovascular Anomalies Combined or Confused with Ventricular Septal Defect

Raymond C. Read, Paul Adams, C. Walton Lillehei, and Richard L. Varco, Minneapolis, Minn.

Between 150 and 200 patients with intracardiac defects have been operated on with the use of various technics permitting total cardiac by-pass. Sixty per cent of these procedures have been for the correction of isolated ventricular septal defects and another 20 per cent for tetralogy of Fallot. The remaining patients comprise a group of more uncommon anomalies. Among these cases have been 18 patients with extra or intracardiac vascular malformations combined with ventricular septal defects. These associated defects have been patent ductus arteriosus, left superior vena cava, interatrial defects, mitral stenosis, truncus arteriosus, coarctation of the aorta, and corrected transposition of the great vessels. Another group of patients with a clinical course resembling ventricular septal defects were later found to have patent ductus arrteiosus, aorticopulmonary window, ruptured sinus of Valsalva, single ventricle, or atrioventricular canal.

Experience has emphasized the importance of making a complete and accurate preoperative diagnosis. Diagnostic thoracotomy is unsatisfactory because frequently the real extent, number, and type of defects present is not realized. At operation certain combinations of defects may be best treated in stages, by a different surgical approach, or with the use of plastic or other grafts. Some malformations may require special perfusion procedures for successful treatment. These clinical cases have been analyzed in retrospect for characteristic signs and symptoms as well as important radiologic and catheterization features which will allow more successful differential diagnosis in the future.

Physiologic Correlations of the Force Ballistocardiograph

Thomas J. Reeves, Lloyd L. Hefner, Ellis Sparks, and William B. Jones, Birmingham, Ala.

Force ballistocardiograms, recorded from an ultra low-frequency suspension utilizing increased coupling of the body to the bed, and an extended range accelerometer, have a complex wave form varying significantly from previously described ballistocardiograms. The extended frequency range of such a system allows visualization of high frequency forces which may be closely correlated with events of the cardiac cycle. Such correlation allows some clarifications of genesis of the ballistocardiogram.

In normals the first visible force is small and inconstant and is termed the F-G wave. The G-H wave is high, with the first peak (H_1) occurring at the time of right ventricular ejection, and the second peak (H_2) occurring at the time of left ventricular ejection. It precedes the carotid upstroke by a constant interval. At the nadir of the H_2-I downstroke there is a small headward peak (J_1) corresponding precisely to the upstroke of the carotid pressure pulse. There are 3 other headward components of the I-J-K complex (J_2, J_3, J_4). A consistent respiratory variation suggests discrete contribution by the right and then the left ventricle. The K nadir is inconstantly seen. There are 2 footward deflections at the end of systole correlating with the 2 components of the second heart sound, cleanly separated when the sound is split. There is a reproducible pattern in early diastole, appearing to have significant physiologic correlation. Atrial systole is marked by a recognizable pattern.

Each of these points have been observed to be exaggerated in certain abnormal conditions. These findings suggest the possibility of more precise physiologic interpretation of the ballistocardiogram.

Coronary Blood Flow and Myocardial Metabolism in Aortic Insufficiency

Timothy J. Regan, Frederick N. Talmers, Raymond C. Christensen, Takashi Wada, and Harper K. Hellems, Detroit, Mich.

The technic of coronary sinus catheterization was employed in 9 patients with severe aortic insuffi-

ciency to determine coronary blood flow (nitrous oxide method) and the myocardial metabolism of oxygen, glucose, lactate and pyruvate. All patients had reduced diastolic pressures (38 to 64 mm. Hg), wide pulse pressures (55 to 139 mm. Hg) and varying degrees of left ventricular enlargement. On the basis of symptoms and hemodynamic alterations, the following groups were apparent: Group I, 3 patients without angina or failure; group II, 2 patients with angina; and group III, 4 patients with failure as manifested by elevated pulmonary capillary pressures (18 to 29 mm. Hg).

Coronary flow in ml./100 Gm. of left ventricle/min. was 91, 100, and 107 in group I; 66, 68 in group II; and 110, 123, 134, and 173 in group III, as compared to a flow of 103 ± 20 ml./100 Gm./min. in 8 normal subjects. There was not a consistent correlation between coronary flow and brachial artery diastolic and/or mean pressures. Arterial coronary sinus oxygen difference was the same in the 3 groups, but left ventricular oxygen consumption in ml./100 Gm. of left ventricle/min. averaged 12.7 in group I; 8.0 in group II; and 18.4 in group III, compared to normal subjects in whom the oxygen consumption was 10.5 ± 2.6 ml./100 Gm./min. Coronary vascular resistance varied widely, but in general was in the high normal range in group II and reduced below the normal range in group III. Glucose, lactate, and pyruvate utilization was the same in the 3 groups and did not differ from normal subjects.

It is concluded that in aortic insufficiency patients, those with angina have a reduced coronary flow and myocardial oxygen consumption, and those in failure, in accord with the Starling concept, have an increased myocardial oxygen consumption supplied by increased coronary flow rather than greater myocardial oxygen extraction.

General and Regional Circulatory Responses to Induced Acidosis and Alkalosis

David W. Richardson and John L. Patterson, Jr., Richmond, Va.

Changes in blood pH are of common clinical occurrence. More common, probably, are changes in regional acid-base equilibria associated with variations in tissue metabolism or with changes in local blood flow secondary to alterations in blood pressure. In the present investigation, responses in the general circulation and in blood flow in the forearm were measured during induced acidosis and alkalosis.

Subjects were 19 normal human volunteers. Forearm blood flow was measured plethysmographically in 31 observations and cardiac output by indicator-dilution (T-1824) in 25 determinations in which pH change of more than .04 units was induced. Acidosis was induced by intravenous infusion of ammonium chloride or lactic acid, and alkalosis by infusion of sodium bicarbonate. In 19 observations, sympathetic blockade of the forearm was produced by phenoxybenzamine (Dibenzyline) injection into the brachial artery.

No change in arterial pressure occurred following infusion of acid or base. Mean cardiac output was not altered by lowering arterial pH an average of 0.08 units, although the individual values increased in 9 of 11 determinations. Elevation in mean pH of 0.13 units was associated with a 36 per cent rise in cardiac index (1.93 to 2.62 L./min./M.^{2}; $p < .01$).

In the unblocked forearm, change in pH in either direction from control was not associated with change in blood flow. Following Dibenzyline, however, acid infusion produced a 30 per cent, ($p < .01$) increase in forearm blood flow (14.8 to 19.3 ml./100 Gm. of forearm/min.); similarly alkalosis was accompanied by a 48 per cent ($p < .01$) increase in forearm flow (13.4 to 19.8 ml./100 Gm./min.).

It is concluded that changes in pH in either direction exert a local vasodilator action on forearm vasculature. When there is a general acidemia or alkalemia these effects are masked, presumably by impulses from the sympathetic nervous system. Dilation of vasculature other than in muscle and skin must account for the increase in cardiac output associated with alkalosis.

Prevalence of Heart Disease in the Population of Baltimore

Dean W. Roberts, Peter G. Meek, and Dean E. Krueger, Baltimore, Md.

The study of chronic illness in Baltimore included a complete diagnostic examination of a subsample of the random sample of the city's population. The findings about the prevalence of heart disease are presented in the paper.

The prevalence of heart disease of all types (excluding hypertension without mention of heart disease) was 96 cases/1,000 population—a rate very much greater than most previously published and which have been based on interview-type morbidity surveys. Coronary artery disease and angina pectoris was found at the rate of 22.5/1,000, hypertensive heart disease at 50.2/1,000, and other heart disease at 23.7/1,000.

Using the American Heart Association classification by functional capacity, over half of all cases were in the group with no limitation of physical activity and an additional 30 per cent had only slight limitation. Only 15 per cent had substantial physical limitations. Similar conclusions result from use of the AHA therapeutic classification.

The age distribution of heart disease was highlighted by the finding that 575 persons/1,000 aged 65 and over have heart disease. The prevalence of coronary artery disease was 10 times as great for persons over age 65 as for persons aged 35 to 64. For the same age groups, hypertensive heart disease was 3 times more prevalent among the aged. Over 65

he rate for hypertensive heart disease was 265/ ,000 and for coronary artery disease, 204/ 1,000.

There was little difference between men and women in the prevalence of all heart disease. Substantial differences in prevalence were found, however, for particular types of heart disease.

Heart disease is substantially more prevalent among whites than among nonwhites. However, "age-adjusted" rates show nonwhites to have more heart disease than whites. Even with "age-adjustments," arteriosclerotic heart disease remains much more prevalent among whites.

Heart disease was more prevalent among persons with annual family income under $2,000 than in the middle income groups, but tended to rise again for income groups $6,000 and over.

Incidence of Rheumatic Fever in San Francisco Children: A Ten-Year Study

Saul J. Robinson, San Francisco, Calif.

The Cardiac Registry maintained by the San Francisco Department of Public Health with the cooperation and aid of the San Francisco Heart Association, has made it possible to keep a record of the incidence of rheumatic fever in children in the years from 1946 through 1955. In addition, this registry has recorded the number of recurrences of rheumatic fever, the number of children hospitalized with this disease, the number of children placed in convalescent homes, and the number of children who are receiving a prophylactic drug for the prevention of recurrences of rheumatic fever in the years 1949 through 1955.

There has been a decrease in the incidence of active rheumatic fever cases reported from 181 in the year 1946 to 56 in the year 1955. The number of cases of rheumatic fever with onset only during each year, and not including those carried over from the previous year, was reduced from 116 cases in 1946 to only 29 in 1955. This marked decrease in cases of active rheumatic fever was not paralleled by a similar decrease in the number of cases of recurrent rheumatic fever in the years 1949 to 1953, but in 1954 there was a decrease from 20 recurrent cases to only 6 recurrent cases in 1954, with only 4 recurrent cases in 1955. This decrease in the number of cases of recurrent rheumatic fever reported was noted after an educational campaign for physicians and lay persons, concurrently with the distribution of a copy of the 1953 bulletin on the prevention of rheumatic fever and its recurrences as published by the American Heart Association, which was mailed to every physician in San Francisco. Simultaneously, prophylactic drugs were made available under the Crippled Children Services Program for those eligible under this program. The San Francisco Heart Association maintained a strong educational program regarding prevention and prophylaxis throughout these years.

The decrease in the number of active rheumatic fever cases has been paralleled by a decrease in the number of children hospitalized with this disease during this period. In 1949 there were 58 children in convalescent homes with the diagnosis of rheumatic fever, but in 1955 there were only 17 such cases. The mortality rate from rheumatic fever in San Francisco has never been high. In 1949 there were 5 children reported as dying from rheumatic fever or its complications. In 1953 and 1954 this community had the enviable record of no deaths in children attributed to rheumatic fever, but in 1955 1 child with rheumatic carditis expired with this disease.

Thus it can be seen that through the use of an active Rheumatic Fever Registry it has been possible to note an encouraging decrease in the incidence of rheumatic fever and its recurrences, with a reflection on the number of children hospitalized and admitted to convalescent homes.

Varieties, Mechanisms and Clinical Significance of the Auscultatory Gaps

Simon Rodbard and Jan Ciesielski, Buffalo, N. Y.

Auscultatory gaps have been analyzed in 75 patients with aortic stenosis, generalized arteriosclerosis, congestive failure or pulmonary disease. In each condition the mechanism is shown to be different. The pattern and size of the gap provide an appraisal of the degree of the abnormality. In aortic stenosis, the cuff pressure at which the gap occurs corresponds exactly to the level of the incisura on the ascending limb of the arterial pulse wave. This is demonstrated by direct measurement and by arteriophonography. The severity of the stenosis is correlated generally with the width of the gap, and the duration of the incisura. This type of gap is related to the reduction in the slope of the upstroke of the pulse wave. Similar mechanisms produce a variable gap near the elevated systolic level in arteriosclerotic heart disease with left heart embarrassment. Gaps in atrial fibrillation irregularly appear with the changes in arterial pressure from beat to beat. The gaps described above are widened by application of a tourniquet below the stethoscopic pickup in accord with the reduced blood flow to the extremity; they are eliminated by reactive hyperemia.

In congestive heart failure or in primary pulmonary disease, the blood pressure may fluctuate markedly with respiration, rising as much as 25 mm. Hg during each expiration. The depth of this fluctuation provides an estimate of the degree of cardiac or pulmonary dysfunction. These respiratory oscillations in blood pressure may produce a pseudo-gap if sounds heard during expiration while the cuff pressure is high, vanish temporarily as the blood pressure falls with the onset of inspiration. Assessment of the gap may thus provide significant and easily available clinical material concerning cardiac function.

Postural Changes in Blood Pressure in the Aged

Manuel Rodstein, New York, N. Y.

Two hundred and fifty individuals, 61 to 91 years of age, were given an orthostatic tolerance test. One-half had symptoms of headache, weakness, dizziness, dyspnea, dimness of vision, lack of concentration, sweating, fainting or vertigo. There were no differences in age range, recumbent blood or pulse pressure between the symptomatic and asymptomatic groups.

In the symptomatic group, only 17 had a fall of more than 25 mm. systolic without predominance of any particular symptom. In the asymptomatic group, only 9 had a fall of more than 25 mm. systolic. In both groups, none had a fall of more than 62 mm. systolic or more than 40 mm. diastolic, or fell to a level of 90 systolic over 54 diastolic or below.

The change in blood pressure on standing exceeded the accepted limits of normal in 58 asymptomatic and 46 symptomatic cases.

Among those with more than a 25 mm. systolic fall, 20 of 26 cases had such etiologic factors present as markedly enlarged varicose veins of the legs, thrombophlebitis, diabetic neuritis, anemia, cerebrovascular disease, parkinsonism and hematomyelia.

It is concluded that there is a common abnormal lability in response to standing in the aged. However, falls of more than 25 mm. systolic or 15 diastolic are infrequent and falls to a level of 90 systolic or 54 diastolic or below are absent in this series.

The presence or absence of symptoms commonly attributed to hypertension in the aged was not related to the height of the recumbent blood pressure. The presence of symptoms commonly attributed to orthostatic fall in blood pressure in the aged was not related to fall in blood pressure on standing except in a small percentage whose systolic fall exceeded 25 mm. In this group symptomatic cases predominated in number, but showed no increased degree of fall in blood pressure.

Vasomotor Activity in the Pulmonary Circulation: Pharmacologic Studies

John C. Rose† and Eric J. Lazaro, Washington, D. C.

Active pulmonary vasoconstriction in response to pressor amines has previously been demonstrated in our laboratory. Are the pulmonary vessels capable of active vasodilatation? How does their sensitivity to pharmacologic stimuli compare to that of the systemic vessels?

The left ventricle was completely by-passed in dogs, using a mechanical pump of controlled output. Left atrial blood was conducted to a reservoir from which it was pumped into the aorta. Right ventricular function remained unaltered. Modification of this system permitted study of drug effects on the "isolated" lesser circulation.

As the drug under study was injected into the pulmonary artery, left atrial blood was temporarily diverted into a second container. The pump continued to supply the systemic circulation from the main reservoir. Thus, the drug traversed only the lungs. Finally, the blood in the temporary container was returned to the system, and the drug effect on the systemic circulation noted.

Acetylcholine in doses of more than 100 μg caused marked pulmonary hypertension. However, this was found to be accompanied by increased airway pressure, signifying bronchoconstriction. In doses insufficient to affect the bronchi, acetylcholine usually directly elicited pulmonary vasodilatation. (Increased pulmonary vascular resistance due to pressor amines was *not* accompanied by increased airway pressure.)

No drug, including norepinephrine, affected the pulmonary vasculature in doses which did not produce systemic effects. Several systemically potent agents (e.g., nitrites, nitroprusside) caused no detectable pulmonary vasomotion.

Conclusions. The pulmonary blood vessels are less sensitive to given pharmacologic stimuli than the systemic vessels. Their true reactions may be masked by bronchomotor activity. However, the pulmonary vasculature is capable of both *active constriction* and *dilatation*. Thus, regional hemodynamic adjustments are possible in the lungs.

Development of a School Health Program for Children with Heart Disease in Chicago

Ira M. Rosenthal, Carl J. Marienfeld, Bess L. Lendrum, and Oglesby Paul, Chicago, Ill.

As 1 phase of its program of community service, the Chicago Heart Association working with the Chicago Board of Health, 4 years ago inaugurated a program of services for the school child with heart disease. The first step was the appointment by the Chicago Heart Association of a cardiac consultant to the Board of Education. This physician has reviewed over 1076 applications for placement in the special school system due to the presence of heart disease, and has advised the Board of Education, the family physician, and in some instances the parents, as to the desirability of such placement. Twenty-two per cent of such referrals have been resolved by continuance in or transfer to the regular school system—a measure psychologically beneficial to the child not needing a sheltered environment and presenting a saving to the taxpayer of approximately $800.00/year/child. Twenty-five per cent of cases, found unsuitable for formal schooling, have been cared for by home teachers. Fifty-one per cent have been recommended to special schools.

The consultant initiated the appointment of a special teacher nurse to assist in working with principals, teahcers, and families in planning within the school system for each pupil with heart disease. This teacher nurse also acted as a liaison between

the private physician or clinic and the school, and assisted in medical referral of pupils with suspected or proved heart disease not under medical supervision. This program proved successful, and now 48 teacher nurses visit each cardiac child, his teacher and, if possible, his family at least once a year. Interpretation of the child's special needs are made to school personnel, and reports of each visit sent to the cardiac consultant for review with school nursing supervisors and social workers. Finally, a vocational guidance and counseling unit has been established.

Decreased Permeability of Capillaries to Protein in Chronic Congestive Heart Failure

Richard S. Ross and W. Gordon Walker, Baltimore, Md.*

Plasma disappearance curves of I^{131}-labelled human serum albumin have been constructed from observations extending over a 14-day period following single intravenous injections into human subjects. A "mean transcapillary exchange rate" can be obtained by assuming that the fall in concentration with time during the first few days results from both the transcapillary equilibration of the labelled material with the extravascular protein pool and the metabolic degradation of the protein. In 11 normal individuals the "mean transcapillary exchange rate" is more closely correlated with the mass of circulating protein ($r = +.7$; $p < .001$) and the plasma volume ($r = +.6$; $p < .02$) than with the serum protein concentration. Capillary permeability to protein increases with a rise in the plasma volume and the total mass of circulating protein. Thus, changing permeability serves to maintain the plasma volume within relatively narrow limits despite wide variation in the total mass of exchangeable protein. In the group of normal subjects, an 8-fold variation in total exchangeable protein is accompanied by only a 3-fold variation in plasma volume. In sharp contrast are the findings in the group of 7 patients with congestive failure. In this group the relationship between "mean transcapillary exchange rate" and plasma volume is reversed ($r = -.6$), the larger the plasma volume the smaller the exchange rate. A significant decrease in the fraction of the total protein which is extravascular ($p < .01$) seems to be a consequence of this decrease in permeability. Thus it appears that the decreased permeability of the capillaries to protein maintains the expanded plasma volume of congestive heart failure.

Hemodynamic Effects of Salicylate

George G. Rowe, George M. Maxwell, Cesar Castillo, Dean A. Emanuel, John F. Brown, and Benjamin Schuster, Madison, Wis.

Hemodynamic observations were made on 10 mongrel dogs before and an average of 22 min. after intravenous administration of 100 mg./Kg. of sodium salicylate. Cardiac outputs were determined by the Fick principle and coronary flow by the N_2O method.

Body oxygen consumption increased 75 per cent ($p < 0.001$) and CO_2 excretion rose 44 per cent ($p < 0.001$). These increases in exchange of respiratory gases were compensated for by increases in the arteriovenous oxygen (+80 per cent, $p < 0.001$) and CO_2 (+44 per cent, $p < 0.001$) differences so that cardiac output was unchanged. Concomitantly, there was an increase in pulmonary ventilation (+64 per cent, $p < 0.01$).

The pulmonary arterial pressure rose (+17 per cent, $p < 0.01$) and pulmonary vascular resistance increased (+17 per cent, $p < 0.02$), but systemic arterial pressure and resistance were unchanged. The arterial-coronary sinus blood O_2 difference increased (+14 per cent, $p < 0.001$) due to a decrease in coronary sinus blood O_2 content (−39 per cent, $p < 0.001$), but the 6 per cent decrease in coronary blood flow/100 Gm. of myocardium was not significant ($p < 0.7$), nor was the 8 per cent increase in cardiac oxygen utilization ($p < 0.6$). Cardiac efficiency was not significantly reduced (−10 per cent, $p < 0.4$).

It is reassuring to know that in spite of its metabolic effects, sodium salicylate, even in this heavy dose, had so little deleterious effect on systemic hemodynamics or myocardial efficiency.

Effects of Tolazoline (Priscoline) Hydrochloride on Cardiodynamics of Patient with Pulmonary Hypertension

Abraham M. Rudolph, Milton H. Paul, Leonard S. Sommer, and Gerald J. Sutin, Boston, Mass.*

Pathologic changes in small pulmonary vessels are frequently demonstrated in patients with pulmonary arterial hypertension with or without congenital heart disease. The possible role of spasm in association with these changes, or spasm of small vessels alone, has not been delineated. Various spasmolytic agents have been tested for effectiveness in relief of possible pulmonary vascular spasm. Tolazoline (Priscoline) hydrochloride, an effective drug for relief of spasm in peripheral vascular disease, has shown some promise as an agent for reduction of pulmonary arterial pressure in patients with pulmonary arterial hypertension.

The effects of acute administration of tolazoline hydrochloride into the pulmonary artery was studied in 10 patients, aged 3½ to 29 years, during the course of cardiac catheterization. All 10 patients had severe pulmonary hypertension with marked increase in pulmonary vascular resistance; 5 had ventricular septal defect, 2 had atrial septal defect, 2 had patent ductus arteriosus, 1 had no other demonstrable cardiac anomaly.

Tolazoline was administered in divided doses (total dose 10–75 mg.) until a definite peripheral vascular effect was noticed, as evidenced by skin flushing. These effects were confirmed in 2 patients

by skin temperature measurements and plethysmographic recording of finger blood flow. Pulmonary arterial, systemic arterial and pulmonary wedge pressures (where feasible) and pulmonary blood flow, were measured before and after tolazoline administration. In 3 patients simultaneous systemic and pulmonary arterial blood flows were determined by insertion of a second catheter to the right atrium.

Nine of the 10 patients showed no significant change in pulmonary vascular resistance following tolazoline administration. In most patients pulmonary arterial pressure was not reduced; in 3 children there was actually a rise of pulmonary arterial pressure associated with a rise of cardiac output. One patient showed a definite decrease of pulmonary arterial pressure with a moderate increase in pulmonary blood flow, and an increased left-to-right shunt, with a moderately decreased pulmonary vascular resistance.

Our studies indicate that tolazoline hydrochloride is of minimal value in reducing the pulmonary vascular resistance in patients with pulmonary arterial hypertension.

Left Ventricular Performance Continuously Analyzed by Electronic Computors

Robert F. Rushmer, Allan W. Lobb, and Dean L. Franklin, Seattle, Wash.

Changes of left ventricular diameter in intact dogs can be recorded continuously by a modification of the sonar technic. Two small barium titanate crystals are sutured on opposite sides of the left ventricle. One crystal is excited by a microsecond pulse and emits a sound wave. The time taken by the sound waves to pass through the left ventricle is monitored 2,500 times/sec., providing a smooth curve of changing ventricular diameter. Effective left ventricular pressure is recorded by means of a small differential-transformer pressure gage mounted at the apex of the heart. With the assumption that changes in recorded diameter reflect changes in ventricular volume, a number of parameters can be measured or computed from the output of these 2 gages including rate of change of diameter, the rate at which work is performed by the myocardium that contributes to the change in dimension (power), the stroke work of the myocardium, the heart rate and the amount of work performed per unit time. These parameters have been continuously recorded during spontaneous activity and experimentally induced responses of intact animals fully recovered from the surgical installation of the gages. For example, during exercise on a treadmill at 3 m.p.h. on a 5 per cent grade, the cumulated work per unit time is promptly increased by increased systolic pressure, greater stroke volume and by tachycardia. Judged from the diameter, the left ventricle appears to function near its maximal diastolic volume in normal resting animals. Stroke volume, as indicated by the changing diameter, may be increased by greater diastolic filling, more complete systolic ejection, or a combination of the 2 during a response to exertion. The response to exertion is not simulated in dogs by the intravenous infusion of epinephrine, norepinephrine, or acetylcholine. Stimulation of sympathetic nerves to the heart produces responses which more closely resemble the spontaneous adaptations observed in intact animals.

Serum Beta-Lipoprotein Studies in the South African Bantu

Herman D. Ruskin, New York, N. Y., Theodor D. Cohn, New York, N. Y., Irving J. Greenblatt New York, N. Y., and Ben M. Bloomberg, Johannesburg, S. Africa.

Because the South African Bantu is almost completely exempt from the consequences of coronary atherosclerosis, a study of the serum β-lipoprotein pattern was made in 304 male and female subjects of various age groups. Blood samples were collected in the Johannesburg area, suitably prepared and then flown to New York where the S_f 12–20 and S_f 20–100 classes of lipoproteins were determined by ultracentrifugation.

Both classes of serum lipoproteins were found to be markedly lower when compared with the "normal" levels for a sample of the New York City white population as determined by the same laboratory. Female subjects exhibit somewhat higher levels of these 2 classes of β-lipoproteins when compared with males, the difference becoming more marked with increasing age since the lipoprotein levels remain constant in the males while they increase moderately in the females. Using the New York City "normal" values, only 9 (4.2 per cent) of 213 Bantu males and 14 (15 per cent) of 91 females had elevated S_f 12–20 levels.

The low serum β-lipoprotein levels appear to be related to the low-fat content of the Bantu diet. While this relationship may be paramount in explaining the freedom from the effects of coronary atherosclerosis exhibited by the Bantu, other factors bear further study. Such factors include the possibility of a protective substance in mealie meal which is the staple article of diet or chronic hepatic dysfunction which may result in disturbance of the androgen estrogen balance as well as subclinical impairment of the clotting mechanism.

Limited Use of Anticoagulants in Acute Myocardial Infarction: Analysis of 1000 "Good Risk" Cases

Henry I. Russek, Staten Island, N. Y. and Burton L. Zohman, Brooklyn, N. Y.

Although it has been established that anticoagulant therapy represents an important advance in the treatment of acute myocardial infarction,

t ere is still no valid evidence to support the con- t ntion that all patients should be treated in this ı anner. Disagreement has arisen as to whether the ı sk of thromboembolism in patients sustaining an ı ncomplicated first attack is sufficiently great to j stify the hazards inherent in the use of anticoagu- l nt drugs. Some authorities assert that it is im- ossible to determine with certainty the prognosis of n acute myocardial infarction during the first 24 r 48 hours, and therefore reject "prognostic classifi- ation" at the onset of an attack as a means of lecting patients for this form of treatment. In an ttempt to clarify this problem, an analysis was ndertaken of the clinical course in 1000 patients vho qualified as "good risks" on the basis of clinical igns and symptoms observed at the first examina- ion following admission to the hospital. The overall nortality rate for this group was found to be only 3.5 per cent and the incidence of fatal thromboem- bolism appreciably less than 1 per cent. In 511 of the 1000 cases, careful scrutiny throughout the entire period of hospitalization to discover evidence of thromboembolic phenomena disclosed the presence of these complications in only 3.7 per cent. All of these episodes moreover, were of a mild nature and not a single instance of cerebral or peripheral ar- terial embolism was encountered. In the entire series of 1000 patients, embolism to the brain occurred in 1 case while embolism to an extremity was not ob- served. Inasmuch as hemorrhagic complications from anticoagulant therapy may equal or exceed any benefits theoretically possible in this low risk group, such treatment must be regarded as neither necessary nor desirable for "good risk" cases. The observations indicate that "prognostic classifica- tion" at the onset of an attack affords a practical and reliable means of selecting patients for this form of treatment in acute coronary occlusion.

Variable Relationship of Pulsus Alternans to Stage of Heart Failure

Joseph M. Ryan, James F. Schieve, Hugh B. Hull, and Beryl M. Oser, Columbus, Ohio.

Three years experience has shown that pulsus alternans may exhibit 3 types of behavior. These are in addition to the well documented disappearance of this phenomenon following digitalis therapy. First, it may be present only with the stress of exercise. This type has been encountered 4 times and hemodynamic data indicate that it may repre- sent myocardial insufficiency which is otherwise clinically unapparent. Second, if it is present at rest, it can be profoundly influenced by changes in the venous return to the heart, being exaggerated by a decreased return and diminished by an increased return. This form has been noted 8 times in patients who were or who had been in heart failure. Third, alternation may disappear as congestive heart failure becomes more severe with further deteriora- tion in myocardial function. Three patients have shown this response. Of particalar interest is 1 pa- tient who has shown 2 different types of behavior. At first he was clinically asymptomatic and demon- strated alternans only after exercise, but 1 year later, when heart failure had become clinically ap- parent, he exhibited a sustained resting alternans that was diminished with effort and exaggerated by tilting.

We have not seen pulsus alternans in the absence of organic heart disease and thus believe myocardial factors peculiar to certain diseased hearts are neces- sary for its production. It would also appear that alternation indicates myocardial insufficiency, but the type of behavior it exhibits depends to some extent on the degree of insufficiency.

Our experience indicates that a patient with a sustained alternans at rest has just as good a prog- nosis as 1 without an alternans, but with a similar type of heart disease and degree of failure. This is at variance with the prognostic implication usually ascribed to this phenomenon.

Right and Left Bundle-Branch Block in Young Healthy Subjects

Sami I. Said and J. Marion Bryant, New York, N. Y.

Incomplete "bundle-branch block" has usually been considered evidence of heart disease. Incom- plete left bundle-branch block is generally thought to indicate a more serious condition than right bundle-branch block.

One hundred subjects, without evidence of heart disease, ranging in age from 18 to 40 years were studied. Simultaneous leads (Sanborn Twin-Beam Electrocardiograph) were recorded from numerous points encircling the chest at the conventional level and at the level of the second intercostal space.

Secondary R-waves, considered as evidence of "incomplete right bundle-branch block," were re- corded in 1 or more leads from sites on the right anterior and lateral chest in 87 subjects. Sites most commonly showing secondary R-waves were above and to the right of V_1. A secondary R-wave was present in V_1 in only 9 cases. In only 4 of these 87 cases did V_R fail to show a late R-wave.

Eleven subjects showed slurring or notching of the upstroke of the R-waves in left ventricular leads ($V_{5, 6, 7}$) and all but 1 had absent Q-waves in the same leads. These findings are compatible with "incomplete left bundle-branch block." Seven of these cases also demonstrated small Q-waves in 1 or more high right precordial leads, further suggest- ing a right-to-left initial activation of the septum.

It is suggested that these findings represent normal variations in the order of ventricular activation rather than "blocks" in bundle-branch conduction. Recognition of these normal variants may prove to be of fundamental value in understanding superim- posed pathologic processes.

Diagnosis of Incomplete Left Bundle-Branch Block

Sami I. Said, Henry M. McLaughlin, and J. Marion Bryant, New York, N. Y.

Incomplete left bundle-branch block is a well-recognized though poorly defined electrocardiographic entity. Its recognition is important, first, because it may mask or simulate the diagnosis of myocardial infarction, and secondly, because its presence is commonly believed to indicate heart disease. However, there is no agreement concerning the diagnostic criteria. The absence of Q-waves in V_5 and V_6 may suggest the diagnosis (Wilson). Slurring or notching of the upstroke of the R-wave in these leads, with or without Q-waves, has also been proposed as indicative of the condition (Sodi-Pallares), whereas small Q-waves in a right precordial lead suggests leftward direction of the initial septal vector.

Simultaneous tracings were taken from the right and left precordium in patients who showed Q-waves in V_5 and V_6, but who otherwise had suggestive findings of incomplete left bundle-branch block; slurring of the upstroke in the same leads, small Q-waves in 1 or more right precordial leads, and initial negativity in right ventricular intracavitary leads "Q-waves" from left precordial leads were found to be preceded by isoelectric periods, or by indistinct initial positive deflections. It is possible therefore, that in these cases, there were no true Q-waves in $V_{5,\ 6}$. This could eliminate the apparent controversy concerning the diagnostic criteria of right-to-left initial septal activation.

It is suggested that the use of simultaneous recording from the right and left precordium may help clarify the electrocardiographic diagnosis in some cases of incomplete left bundle-branch block.

Is There a Diastolic Suction of the Cardiac Ventricles? Demonstration of Negative Pressure Developed by the Ventricles in Diastole

Peter F. Salisbury, Los Angeles, Calif.

In anesthetized, closed-chest dogs, pressures in the right ventricle and the femoral artery were sensed with appropriate cannulas on Statham strain gages and registered on a multichannel direct writing oscillograph. An intravenous drip of 5-hydroxytryptamine was administered at the rate of 0.015 mg./Kg./min. The femoral pressure and the systolic pressure of the right ventricle were elevated by the infusion, but the diastolic pressure of the right ventricle was not changed appreciably. While the infusion continued, hexamethonium, 5 mg./Kg., was injected intravenously. The hexamethonium injection decreased femoral arterial, and right ventricular systolic pressures by about 20 mg. Hg; the most striking change following hexamethonium injection consisted in immediate lowering of the right ventricular diastolic pressure, which reached negative values of −50 cm. water. This observation is interpreted as demonstrating the diastolic suction of the right ventricle, which becomes manifest as a negative diastolic pressure in a vigorously contracting ventricle when there is a reduced venous return.

Prolonged Surgical Exposure of the Aortic Valve with Total Body Perfusion and with Antegrade and Retrograde Perfusion of the Coronary Circuits

Peter F. Salisbury, Leon Morgenstern, Maurice M. Hyman, and David State, Los Angeles, Calif.

The safety of aortic valve surgery and other interventions which necessitate incision of the ascending aorta is greatly enhanced by separate perfusion of the myocardium and the peripheral circulation. In this arrangement the total venous return is routed through a system of blood pumps—gas exchange apparatus ("artificial heart-lung"). Part of the arterialized blood is injected into the subclavian or femoral arteries in a central direction. The ascending aorta is clamped and the heart is then bloodless, except for the small flow from the bronchial arteries. Various means of achieving separate perfusion of the myocardium have been explored. Perfusion of the left coronary artery through its aortic ostium is often impossible because of the origin of the septal artery close to the septum. In dogs arterialized blood can be injected into the coronary sinus and will then supply the territory served by the left coronary artery; the left ventricle remains well oxygenated and maintains coordinated contractions when supplied with blood by retrograde perfusion of the coronary sinus; 40 per cent of the retrograde flow issues from the left coronary ostium. The right ventricle remains cyanotic upon retrograde perfusion because it has no coronary veins. It can be perfused by cannulation and perfusion of the right coronary artery, through its aortic ostium.

Experimental Pulmonary Embolism: Effect of Variation of the Arterial Pressure on the Hemodynamic Changes and the Clinical Course After Standard Embolization of the Pulmonary Artery

Peter F. Salisbury and David State, Los Angeles, Calif.

In open-chest dogs, a standardized pulmonary embolism syndrome was reproduced by controlled distension of a balloon in the pulmonary artery or by the insertion of large plastic spheres into the pulmonary artery via an incision in the right auricular appendage.

Standard pulmonary embolization in dogs with an arterial blood pressure of 70 mm. Hg systolic or less, resulted in progressive hypotension, right ventricular failure and death. After standard embolization dogs which exhibited complete incompetence of the

right ventricle and which had an arterial pressure of 10 mm. Hg could be rescued by therapeutic maneuvers which elevated the arterial pressure. After revival of the embolized dogs, standard embolization was repeated in the same animal but with the arterial pressure above 70 mm. Hg. With the systolic arterial pressure above 70 mm. Hg, standard embolization of the pulmonary artery is not lethal insomuch as the right ventricle is capable of generating contractile force sufficient to overcome the obstruction in the pulmonary artery, and the circulation remains adequate.

The results are of clinical significance, which will be discussed.

Influence of Personal or Family History of Rheumatic Fever on Susceptibility to Group A Streptococcal Infection

Herbert A. Saltzman, San Antonio, Tex., Norbert Schalet, Syracuse, N. Y., and Harold B. Houser, Syracuse, N. Y.

Twenty-nine hundred and seventeen male recruits entering 10 weeks of Air Force training were investigated by questionnaire and subsequent interviews for personal or family histories of rheumatic fever. Ninety-eight men exhibited 22 personal, 72 family, and 4 combination histories. Bunkmates without positive histories served as controls. Weekly throat cultures and periodic blood specimens for anti-streptolysin 0 determinations were obtained. Eighty-three individuals with a rheumatic fever history and their controls were suitable for complete study and data from these men have been analyzed for acquisition of group A streptococci and significant rise in anti-streptolysin 0 titer.

Of 34 acquisitions of group A streptococci occurring for the first time in 1 member of the pair ("rheumatic" and his control), 15 appeared in the "rheumatic" member and 19 in the control member. Lancefield type 18 was the predominant type and occurred with similar frequency (6 times) in each group. Persistence of group A streptococci in the throat culture for 2 weeks or longer occurred in 8 "rheumatics" and 10 controls. Significant antistreptolysin rises of 2 tubes or greater occurred in 11 "rheumatics" and 13 controls. The rheumatic group, with an initial mean antistreptolysin titer of 98 units compared to 78 units for the control, had a mean increase in titer of 21 units compared to a mean increase in titer of 31 units in the control group. Acute rheumatic fever occurred 3 times among the "rheumatics" and not at all in the controls.

The results indicate that individuals with a personal or family history of rheumatic fever do not exhibit an increased susceptibility to group A streptococcal infection when compared to matched controls with similar exposure opportunities. It is indirectly suggested that the high familial incidence of rheumatic fever may be the result of either greater exposure or altered reaction to group A streptococci.

Simultaneous Catheterization of the Right and Left Sides of the Heart

Philip Samet, Miami Beach, Fla., Robert Litwak, Miami, Fla., William H. Bernstein, Miami Beach, Fla., and Anna Rosenthal, Miami, Fla.

Simultaneous catheterization of the right and left sides of the heart has been performed in 15 subjects with mitral or aortic stenosis. Several patients have also been investigated postoperatively. Semiquantitative evaluation of the degree of mitral or aortic stenosis is feasible via determination of cardiac output and the mean diastolic left atrial-left ventricular pressure gradient or the mean left ventricular-systemic arterial gradient respectively. The former has varied from 0–12 mm. Hg in symptomatic subjects with auscultatory evidence of mitral stenosis. The latter ranged from 31–68 mm. Hg. Cardiac indices were generally reduced at rest with an inadequate rise during exercise. The demonstration of valvular insufficiency is more difficult, but is possible when moderately severe degrees of insufficiency exist. Combined heart catheterization permits identification of the cause of pulmonary hypertension, i.e., left ventricular failure or mitral stenosis with block, or increased pulmonary vascular resistance. The necessity for dependence upon mean "pulmonary capillary" pressure as a reflection of left atrial pressure is obviated.

Right heart catheterization was performed in the usual manner in the supine position, in the basal postabsorptive state. Steady state pressure and flow measurements were made at rest, during exercise, and recovery. Subsequently 50–100 mg. of Demerol was given. Left heart catheterization was then performed via a modification of the posterior percutaneous puncture technic of Fisher. Two 6-inch no. 17T thin-walled styletted needles were inserted in to the left atrium. Polyethylene tubing was passed through these needles into the left atrium and ventricle. On occasion catheterization of the aorta was accomplished. Simultaneous pressures were then obtained (from the same baseline, and at identical strain gage sensitivities) from the left atrium, left ventricle and pulmonary artery, or left atrium, left ventricle and brachial artery, at rest, during exercise, and recovery.

Prolonged Residence in Miami, Florida, of Children with Rheumatic Fever: Five to Ten Year Follow-up

Milton S. Saslaw, Francisco A. Hernandez, and Hazel E. Randolph, Miami, Fla.

Follow-up medical and social data were collected on rheumatic fever children, expatients of the National Children's Cardiac Hospital, Miami, Florida.

Forty-eight children had been discharged after hospitalization, 10 or more years ago; 102 additional children had been discharged 5–10 years ago. All 150 were diagnosed as having subacute or early convalescent rheumatic fever or rheumatic heart disease. A 4-month stay was considered arbitrarily as a minimum for inclusion in the survey. Average duration of hospitalization was 20 months.

Information was available on 133 (88.7 per cent) children. Nine had died. Basis of the present report is on the remaining 124 expatients. Of these, 98 left Florida after their stay in Miami to return to their homes; 84 went to New York, New Jersey, Pennsylvania or Massachusetts. Present average age of the 10 year group is 24.2 years; of the 5–10 group, 19.4 years. Twenty children had recurrences, only 2 of which occurred in Florida. No physical limitation was imposed on 81, while 24 more were restricted only from competitive sports; 19 required moderate to marked decrease in activities.

Detectable heart damage was absent in 54, minimal or questionable in 32, and moderate to marked in 38.

Of 16 girls in the 10 year group, 11 are married, and 7 have borne children successfully.

Educational attainments of the entire group are attested to by the data collected: 27 are students in elementary and high schools, 81 are high school graduates. Of the 81 graduates, 4 have had some college training, 30 are college or professional school students, and 8 are college graduates.

Expatient occupations include an author, teacher, physician, lawyer, accountant, optometrist, pharmacist, engineer, draftsman, nurse, music director, secretary, clerk, T.V. serviceman, auto mechanic, barber, chemist in medical research, radar operator, U. S. Army medical corpsman, factory worker, publishing executive, sociologist, and psychologist.

Comparison of the Epicardial and Body Surface Electrocardiographic Q-Waves Caused by Subendocardial and Transmural Ventricular Scars in Dog and Man

John J. Sayen, Warner F. Sheldon, and Charles C. Wolferth, Philadelphia, Pa.

Studies of the pathologic physiology of coronary disease with special reference to localized ventricular muscle lesions and their electrocardiographic reflection have been carried on in man by clinicopathologic correlation, and in the dog by experimental coronary artery obstruction with survival. In dogs, while epicardial electrocardiographic patterns provided very limited information in acute localized ischemia and early infarction, they were of great value in locating healed scars. Even when these were limited to the inner muscle layers, significant Q-waves were recorded over their full extent, unless the scar was entirely confined to the septum. On the dog body surface only transmural lesions were regularly reflected.

The scars produced by single arterial branch ligation in dogs, however, differ from the healed infarcts of man in tending to spare the left ventricular apex and in being confined to the subendocardial muscle layers only when very small in extent. The scars found at necropsy in man differed considerably from those produced in experimental animals, being more commonly widespread, often entirely confined to the inner muscle layers, and frequently involving the apex.

In man, scars affecting the anterior left ventricular apex, whether transmural or subendocardial, were commonly associated with diagnostic QRS-complex pattern breaks in the precordial leads. In the absence of apical involvement, body surface electrocardiographic abnormalities attributable to scar were rare, except for certain massive transmural posteroseptal and right ventricular lesions. These failures of body surface reflection, which contribute a major cause of the diagnostic deficiencies of the electrocardiogram in coronary disease, seem unlikely to be due to lack of significant epicardial abnormality in the light of our experimental results. Studies in progress aim at producing scars in dogs more closely resembling those characteristic of man, and collecting information during surgical procedures in man regarding the epicardial surface reflection of scars for ultimate necropsy correlation.

Precipitating Factors in Coronary Disease

Sidney Scherlis, Baltimore, Md.

Atherosclerosis is generally accepted as the pathologic basis for coronary occlusion in 95 per cent of cases. Since atherosclerosis is a gradual process, how can one explain the apparently sudden clinical onset of acute coronary thrombosis? A review of our experiences reveals that most patients had "premonitory symptoms" for days or weeks prior to the acute severe episode. These symptoms usually consisted of episodes of anginal discomfort, dyspnea, vertigo, chest discomfort, weakness, or perspiration. The intermittency and inconsistency of these symptoms, and the absence of clear-cut relationship to activity in many cases suggests factors other than gradually progressive sclerosis. A background of "overworry" was more common than one of overwork; emotional tensions seemed to be reaching a crescendo at the time of the "heart attack." Some patients had "heart attacks" complicating acute gall-bladder disease, others upon being told disturbing "news." A normal electrocardiogram was a frequent finding early in an acute coronary episode. Some of the patients treated at this stage failed to develop evidence of myocardial infarction; of these, some subsequently had angina on exertion, others no discomfort. The patients with angina, with or without prior acute coronary thrombosis, frequently had

ngina related to meals, cold, straining at stool and/or excitement.

These observations suggest hormonal or neurogenic (vagal ?) factors, not only in angina pectoris, but also in the precipitation of acute coronary thrombosis in persons predisposed by reason of atherosclerosis. This would explain acute "heart attacks" on the basis of a gradually progressive atherosclerosis, plus acute precipitating factors as noted. This reasoning was applied clinically in the use of atropine sulfate in many of these patients, with good results in preventing angina pectoris, and in apparently minimizing the damage following acute coronary occlusion.

Etiology of Atrial Fibrillation and the Mechanism of its Perpetuation

Jakub G. Schlichter, Chicago, Ill.

In this report our experience in man and dog is presented relating to the etiology of atrial fibrillation and the mechanism of its perpetuation. Vagal stimulation and anoxia are the main etiologic factors in the initiation and perpetuation of atrial fibrillation.

Vagal stimulation (mechanical and chemical) may induce atrial fibrillation. Acetylcholine injected directly into the blood stream was used in our experiments to produce chemical vagal stimulation. Moderate anoxia reduces the threshold of the atria to the initiation of fibrillation, but does not induce this arrhythmia per se; marked anoxia, on the other hand, increases the threshhold to fibrillation.

Anoxia of the atria was found or produced: (1) by interference with or obstruction of its vascular supply, (2) by a decrease in the amount of oxygen carriers, (3) by a decreased O_2 content of the blood due to anoxic anoxemia, and (4) by interference with tissue respiration.

The relationship between vagal stimulation and anoxia can be plotted in a graph and on this correlation the cause of the perpetuation of atrial fibrillation demonstrated. The clinical implication of these findings and the therapeutic approach to this problem are illustrated and discussed.

Mechanism for the Regulation of Urea Excretion in Ruminants and its Relationship to the Control of Urea Excretion in Other Mammals

Bodil Schmidt-Nielsen† and Herschel V. Murdaugh, Durham, N. C.

In the camel the urea excretion on a low protein intake can decrease to very low values (2 mg./Kg. body weight/day). The reason is that in ruminants all essential and nonessential amino acids can be synthesized by the bacteria of the rumen which utilize urea as a nitrogen-source. A combination of growth and low protein intake causes the urea U/P ratio to decrease to values as low as 4 to 6, which is only slightly higher than the osmolar U/P ratio. This occurred on low urine flows, i.e., high tubular reabsorption of water.

In work with sheep we have found a similar relationship between urea excretion and protein intake. We also included studies of the urea excretion during water diuresis and osmotic diuresis. The findings on low protein diet support a hypothesis, already proposed by 1 of the authors (B. Schmidt-Nielsen), that the fraction of urea which diffuses back in the tubules is dependent on urine flow and ADH, and is much greater at low urine flow than has hitherto been assumed. In the sheep as well as the camel on normal protein intake the urea clearance and urea U/P ratios (at low urine flows) are up to 50 times as high as the values found on low protein intake. This supports the hypothesis that an active mechanism for secretion of urea is operating distally in the nephron or in the collecting duct and that this secretion is regulated according to need. Data from other mammals can also be explained by this hypothesis.

Electronic Generation and Comparison of Resolved Scalar, Vector, and Spatial Vector Electrocardiographic Leads from Several Presumably Orthogonal Lead Systems

Otto H. Schmitt, Minneapolis, Minn.

The cube and tetrahedron derived spatial vector lead systems have enjoyed a degree of acceptance as practical approximations to orthogonality and normality in vector electrocardiography, and have even been considered by some to be essentially interchangeable. Recent studies in this laboratory utilizing homogeneous torso models with precisely positionable electric current dipoles to simulate distributed heart dipole sources, have shown that these lead systems display severely variable transfer impedance within the heart volume and so are inadequate. Several substitute compensated lead systems have been devised, however, which tend to converge toward a common result and promise to give a sound theoretic basis for electronic generation of any desired directional lead components in 1, 2, or 3 orthogonal directions without shifting of electrodes on the patient. It has not yet been clearly demonstrated, however, whether tissue inhomogeneity, which is discounted in the model measurements, will seriously interfere with the accuracy of 1 or more of these new systems or whether they will ultimately be so good that body shape correction factors can usefully be applied. A flexible electronic system will be described whereby an existing scalar, vector, or stereovector electrocardiograph can be converted instantaneously to *any* "orthogonal" lead basis by means of interchangeable plug-in network units without other readjustment. The simplified resolver which automatically generates any chosen directional vector components will

also be described. A comparison of the model results in the computer results on chosen normal subjects using at least 2 representatives of each major type of spatial lead system, will be presented to demonstrate the superiority of the new compensated leads in terms of an homogeneous model, and yet show that body-inhomogeneity threatens to limit the practical value of making body shape corrections.

Evaluation of the Apical Systolic Murmur by Phonocardiography

Mortimer L. Schwartz, Maplewood, N. J., Anupam S. Desai, Jersey City, N. J., and Jiro Nakano, Jersey City, N. J.

The phonocardiograms of 87 patients with apical systolic murmurs were analyzed. Tracings were taken on 45 persons with rheumatic heart disease, 35 with hypertensive and/or arteriosclerotic heart disease, and 7 with congenital heart disease. Murmurs were analyzed according to frequency, time of occurrence, duration and form.

Fifty-three per cent of the cases of rheumatic mitral insufficiency were found in the frequency range of over 175 cycles per sec. An additional 33 per cent were found between 151 and 175 c.p.s. Eighty-six per cent of systolic murmurs associated with hypertensive and/or arteriosclerotic heart disease were found in the range below 150 c.p.s. In no instance was a systolic murmur of over 200 c.p.s. found to be due to hypertensive and/or arteriosclerotic heart disease.

Effect of Pentolinium Tartrate on Cardiovascular Hemodynamics

Ralph C. Scott, Samuel Kaplan, William J. Stiles, Te-Chuan Chou, and Richard W. Booth, Cincinnati, Ohio.

The hemodynamic effects of pentolinium were studied in 8 patients. Three patients had systemic hypertension, 3 mitral stenosis, 1 chronic cor pulmonale, and 1 was normotensive.

Cardiac catheterizations were performed in all patients. All measurements were made with the patient recumbent, and the head of the table upon which the patient was lying was raised 20° from the horizontal. Two resting cardiac output determinations and pulmonary artery, pulmonary "capillary," and brachial artery pressure measurements were obtained. Four to 8 mg. of pentolinium were given intramuscularly. After 30 min. the cardiac output and pressure measurements were repeated.

Following pentolinium, the patients with systemic hypertension showed a decline in brachial artery pressure and cardiac output, no consistent change in peripheral or pulmonary resistances, and no change in pulmonary artery pressure.

The cases of mitral stenosis after pentolinium had no change or a decrease in cardiac output, peripheral resistance, and pulmonary artery pressure; the change in pulmonary vascular resistance was variable.

Following pentolinium, the case of cor pulmonale showed no change in cardiac output, a fall in systemic pressure and peripheral resistance, and no change in pulmonary artery pressure or vascular resistance.

The normotensive subject after pentolinium exhibited a fall in systemic pressure, cardiac output and peripheral resistance, no change in pulmonary artery pressure, but an increase in pulmonary vascular resistance.

In this study it was found that: (1) pentolinium caused no change or a fall in cardiac output, (2) the fall in systemic pressure was due to a decline in cardiac output and/or peripheral resistance, (3) the systemic pressure frequently fell while at the same time the pulmonary vascular resistance rose, resulting in no change in pulmonary artery pressure, and (4) the 1 instance of decrease in pulmonary hypertension was due to decrease in pulmonary vascular resistance.

Syndrome of High Interventricular Septal Defect with Unsupported Aortic Valve Cusp

Ralph C. Scott, Johnson McGuire, Samuel Kaplan, and Robert S. Green, Cincinnati, Ohio.

The syndrome of high interventricular septal defect with an unsupported aortic valve cusp producing aortic insufficiency has created surprisingly little interest. The correct diagnosis of this condition is of particular importance since it may be easily confused with patency of a ductus arteriosus.

During the past 2 years we have had the opportunity to observe 5 cases of what we believe to be examples of this entity. The patients range in age from 3 to 37 years.

The diagnosis was confirmed by autopsy in 1 case; in the remainder, the results of cardiac catheterization, aortography, or surgical exploration supported the diagnosis.

There was usually a history of exertional dyspnea and frequently of congestive failure. There was no history of cyanosis. The positive physical findings consisted of an enlarged heart, a loud systolic murmur heard maximally in the left 2–4 interspaces, and a high-pitched diastolic murmur transmitted down the left sternal border. A continuous murmur was heard in 1 case. The pulse pressure was wide in all cases. Cardiac fluoroscopy revealed an enlarged heart with a prominent pulmonary arc segment, pulmonary over-circulation, and dynamic pulsations of the aorta. The electrocardiogram showed left ventricular hypertrophy in all cases and concomitant right ventricular hypertrophy in 1 case.

Cardiac catheterization revealed pulmonary hypertension and the presence of arterialized blood either in the right ventricle or in the pulmonary artery. In 2 cases in which cardiac catheterization

suggested the possibility of a patent ductus, retrograde aortography excluded the presence of a ductus.

The clinical differential diagnosis of this syndrome from patent ductus, rheumatic aortic insufficiency, or other congenital lesions producing systolic and diastolic murmurs at the base of the heart may at times be extremely difficult. Since surgical correction of ventricular septal defects is now being attempted, recognition of this syndrome is important.

Austin Flint Murmur: Its Clinical Differentiation from the Murmur of Mitral Stenosis, with Emphasis on Surgical Case Selection

Jack P. Segal and W. Proctor Harvey, Washington, D. C.

The Austin Flint murmur is often confused with that of mitral stenosis. With the advent of surgical correction for aortic insufficiency as well as mitral stenosis, it is essential to determine which patients with rheumatic aortic insufficiency have associated mitral stenosis. Contrary to the usual teaching, it is usually possible to differentiate the Austin Flint murmur from that of mitral stenosis by means of specific clinical criteria. These criteria are based on evaluation of over 300 patients with free aortic insufficiency.

The Austin Flint murmur is usually associated with the following clinical features: predominant male sex, absence of hemoptysis, and low diastolic pressure with classical peripheral signs of free aortic insufficiency. The rhythm is normal sinus, apical first sound faint, pulmonic second sound normal, ventricular diastolic gallop almost always present, and opening snap absent. The rumble (Austin Flint) is usually accentuated in mid-diastole. There may be generalized posterior esophageal displacement and the electrocardiogram shows left ventricular hypertrophy and frequently first degree A-V block.

On the other hand, mitral stenosis occurs predominantly in females and hemoptysis is not infrequent. Atrial fibrillation is common, the apical first sound increased, and an opening snap present. With sinus rhythm the rumble is usually presystolic. Esophageal displacement is localized.

In combined aortic insufficiency and mitral stenosis, the patients are usually female and hemoptysis is not uncommon. The blood pressure and peripheral pulses are classical for aortic insufficiency, but the auscultatory findings at the apex are typical of mitral stenosis.

Mitral stenosis may be incorrectly diagnosed when the P-R interval is short, particularly with a rapid rate, since in this situation the Austin Flint rumble may be presystolic and the apical first sound increased. The relationship of rate and P-R interval to the location of the Austin Flint murmur will be discussed.

Normal QRS Loop Observed Three Dimensionally Using the Frank Precordial System

George E. Seiden, Philadelphia, Pa.

The 7 electrode and resistive adding network of Frank, has been shown to yield reasonably orthogonal QRS components of approximately equal normalization for human subjects with dipole locations within a 5 x 5 cm. square area at midventricle level. In this study the Frank system was employed to record from 85 normal individuals ranging in age from 20 to 58 years. By use of an electronic resolver, 3 dimensional QRS loops were rotated to be viewed edgewise, and then so as to be seen broadside, irrespective of the spatial position of the loops. The azimuthal angles, ϕ, and elevation angles, θ, required to view the loops perpendicular to their planes from above and the left were recorded.

QRS loops studied in this fashion were remarkably uniform, and were relatively planar in all but 1 instance. Planarity, expressed as the ratio of edgewise width to the long axis of the broadside view, averaged 0.11 with a standard deviation of 0.05. Broadside views of loops were invariably open, without crossover. Uniformly there was initial and terminal delay in the trace; all loops were transcribed counter-clockwise as viewed from above and the left. Openness of the broadside loops, expressed as the ratio of width to length, averaged 0.6 with standard deviation of 0.2. Individual variations in azimuthal and elevation angles varied considerably; ϕ averaged 90° with standard deviation of 30°, θ averaged 50° with standard deviation of 18°.

These data suggest that with improvement in validity of recording orthogonal QRS components, together with the ability to observe the loop broadside regardless of its spatial position, "normal variations" may be appreciably reduced, and consequently abnormality better defined. More cases are being collected to ascertain the degree of spread of this data due to age and other parameters.

A Preliminary Report of Combined Mecamylamine-Reserpine Treatment in Severe Hypertension

Alfred M. Sellers and John A. Mitchell, Philadelphia, Pa.

Mecamylamine (Inversine) a secondary amine, is a ganglionic blocking agent almost completely absorbed from the gut. This minimizes the possibility of acute hypotension resulting from accumulation of the drug, as may occur with other poorly absorbed ganglionic blocking agents.

Mecamylamine was administered orally to 20

severely hypertensive patients. The dose ranged from 7.5 to 17.5 mg., averaging 8 mg./day; its duration of action was 6 to 8 hours. To potentiate the hypotensive effect and decrease the constipation produced by mecamylamine, 17 of 20 patients also received reserpine 1.0 mg. twice daily.

Nine patients classified Smithwick group 4 had an average fall of 25 mm. mean arterial blood pressure (MABP) supine and 31 mm. MABP erect. The average duration of follow-up was 13 weeks. Two patients, Smithwick group 3, had an average fall of 27 mm. MABP supine and 37 mm. MABP erect after 4 months. Nine patients in Smithwick group 2 had an average fall of 16 mm. MABP supine and 17 mm. erect; average follow-up was 13 weeks. For all 20 patients the MABP fall was 19 mm. supine and 25 mm. erect.

Constipation occurred in 16 of 20 patients and was tolerated in all but 1, who discontinued therapy for this reason. Reserpine seemed to decrease constipation; however most patients required laxatives. Three patients described occasional blurred vision and dry mouths.

Because of almost complete absorption from the gut, mecamylamine allows more predictable dose-effect relationship than do other similar agents which have been used in the treatment of hypertension. Combined mecamylamine-reserpine therapy appears to produce lower blood pressures and causes fewer side effects than either agent used alone. Continued evaluation is necessary to determine its merits for long-term treatment and prevention of progressive vascular damage.

Hemodynamic Patterns in Cardiac Failure and their Prognostic Significance

Arthur Selzer, San Francisco, Calif., Donald J. McCaughey, Birmingham, Ala., Arthur O. Stone, San Francisco, Calif., and Carl L. Ebnother, San Francisco, Calif.

A series of 38 patients in cardiac failure caused by various lesions primarily affecting left ventricular function was studied by means of cardiac catheterization. The series included 12 patients with hypertensive cardiovascular disease, 17 patients with arteriosclerotic coronary heart disease, 5 with left sided valvular lesions (excluding mitral stenosis) and 4 with failure due to other causes. Hemodynamic studies were performed at the time when the initial symptoms and signs of cardiac insufficiency were brought under reasonable control, usually 1 to 3 weeks after hospital admission.

Hemodynamic studies revealed 3 main patterns: (1) Patients whose circulatory dynamics at the time of the study returned to normal or almost normal levels; (2) patients who had low cardiac output and/or inadequate response to exercise; and (3) patients who showed primarily increased pulmonary resistance.

A clinical analysis of the patients regarding etiologic factors, clinical findings, the severity and duration of symptoms prior to hospital entry, the response to therapy and the long-range follow up revealed the following relationships between these factors and the hemodynamic patterns: (1) Hemodynamic patterns could not be predicted from the clinical picture, except in extreme cases; (2) severe pulmonary hypertension due to increased pulmonary vascular resistance developed in some patients but showed no relationship to the etiology, duration or severity of cardiac failure; and (3) regardless of the severity and duration of the initial attack, cases with the least deranged circulatory dynamics tended to respond best to therapy and often stayed well with minimal maintenance therapy. Those with most severe circulatory derangement responded poorly to treatment and remained mostly in chronic cardiac failure.

Study of Retinal Vascular Reactivity

Herbert O. Sieker and John B. Hickam, Durham, N. C.

The appearance of retinal arteries and veins is a valuable clinical aid in evaluating degenerative vascular diseases. Studies of normal and pathologic reactivity in these arteriole and venule size vessels have been limited. It is possible, however, with eyeground photographs to determine accurately the response of retinal vessels to change in blood gas tensions and maneuvers which may alter the retinal circulation. The results are expressed as per cent change in vessel diameter on going from control to experimental situations. The data present mean changes in 10 to 20 normal subjects for each experiment.

The retinal arteries and veins constricted (11.6 ± 4.7 per cent and 14.9 ± 6.5 per cent) on going from air breathing to 100 per cent oxygen breathing. Both dilated (10.1 ± 1.0 per cent) with change from air to 10 per cent oxygen. Alteration of arterial size occurred within 1–2 min., but venous alterations lagged by 3–4 min. Vascular reactivity of similar magnitude occurred even with stellate block.

With change from standing to recumbency, the arteries and veins constricted (10.1 ± 3.9 per cent and 7.6 ± 4.0 per cent) and dilated by a similar magnitude with standing again. Effects of oxygen breathing and recumbency were cumulative. Engorgement of the head by venous neck cuff did not alter retinal vessel size or impair vascular reactivity to change in arterial oxygen tension.

Pressure exceeding arterial diastolic pressure was applied externally to the eye for 10–15 sec. Thirty sec. after release of pressure, the retinal arteries and veins dilated (13.8 ± 5.9 per cent and 18.0 ± 6.8 per cent) when compared to the control, even with high or low arterial oxygen tension.

The data presented indicate that changes in

blood gases and retinal circulation alter retinal vessel size. The evidence suggests that the retinal circulation is continuously adjusted under local control to maintain a constant retinal oxygen tension. It is postulated that alteration of these mechanisms may be a factor in development of retinopathy in vascular disease.

Myocarditis Due to Common Respiratory Viruses

Earl N. Silber, Alfred Pick, and Albert Milzer, Chicago, Ill.

During the period from 1950–1956, viral and rickettsial serologic studies were performed on all patients admitted to Michael Reese Hospital in congestive heart failure without obvious etiology, or who showed clinical or electrocardiographic evidence of myocarditis during or following recovery from an acute febrile infection. Eight patients showed a significant complement fixing antibody titer rise (fourfold or greater) in convalescent serum specimens. Three patients were positive for influenza B; 1 for influenza A; 1 for influenza A-prime and 1 for combined influenza A and B infection. One patient with atypical pneumonia had a significant titer of cold agglutinins and the eighth patient was positive for the psittacosis-lymphogranuloma venereum group.

In 4 additional patients the diagnosis of a virus infection was presumptive because, although a significant titer for influenza B or cold agglutinins was obtained, no rise in antibody titer was seen. In 9 other patients, a clinical picture of postinfectious myocarditis similar to the above group was present but no positive viral studies were obtained. In none of these was another etiologic factor for heart disease demonstrable. These are included in the presumptive group.

Two patients died with an acute myocarditis. A histologic picture compatible with a virus myocarditis was present and other etiologies were excluded.

In all of the 21 surviving patients other etiologic bases for cardiac disease have been excluded insofar as clinical and laboratory criteria permit. All patients have been followed to the present time.

The clinical picture in these 23 cases was either that of: (1) an acute fulminating myocarditis, (2) acute with complete recovery, (3) protracted with exacerbations and remissions and ultimate complete recovery, or (4) chronic myocarditis.

Special features of these myocarditides and their implications in clinical cardiology are discussed.

Role of Posture in Cardiovascular Disease

Jacob J. Silverman and Siegfried Salomon, Staten Island, N. Y.

Posture in man is maintained by a delicate balance of complicated reflexes. A disturbance of this balance is reflected swiftly in a wide variety of circulatory manifestations. It is the purpose of this paper to discuss a number of postural syndromes of interest to the cardiologist.

The following postural syndromes are of clinical significance and are discussed in detail: vasodepressor syncope, orthostatic hypotension, carotid sinus syncope, drug syncope, heart failure, pericardial effusion, angina decubitus, postural syndromes in congenital heart disease, left lateral hypotensive syndrome, syndrome of postexertional orthostatic hypotension, air embolism, ball valve thrombus or tumor of left atrium, orthostatic hypertension, orthostatic albuminuria, orthostatic hypernatremia, postural peripheral vascular disorders, and various postural electrocardiographic patterns and arrhythmias.

Postural studies require no special equipment and can easily be performed at the bedside. Unless the cardiologist is alerted to the importance of postural influences many diagnoses will be overlooked or misinterpreted.

Effect of Respiration on Spatial Mean QRS and T Vectors

Ernst Simonson and Otto H. Schmitt, Minneapolis, Minn.

In 30 healthy men the mean spatial QRS and T-vectors were determined in mid-respiration (basic position), deep inspiration, and full expiration. The vectors were constructed from frontal and horizontal plane scalar electrocardiograms by means of a mechanical vector analyzer, and expressed in terms of azimuth (H°), elevation (V°), magnitude (Mag.), and angle between spatial vectors dA°. During deep inspiration, the QRS and T-vector azimuth moves in opposite direction in normal subjects: QRS-H° moves posteriorly, T-H° anteriorly; these changes are statistically highly significant ($p < 0.001$). There is also a discrepancy in the change of QRS and T-elevation: QRS-V° moves significantly downward ($p < 0.001$), while T-V° does not change significantly. Theoretically, the magnitude of spatial vectors and the angle between them should be insensitive to positional changes, but the changes (increase as well as decrease) of QRS-Mag., T-Mag., and dA° during deep inspiration exceeded the error of measurement (1.0 mm., 0.5 mm. and 5°, respectively) in the majority of the normal group. There was no correlation between the position of spatial vectors in midrespiration and their changes in inspiration. The changes persisted somewhat after the end of full inspiration. In full expiration, QRS-H° moved anteriorly and QRS-V° moved upward ($p < 0.05$). These changes were smaller than those in inspiration, but significant at the 1 and 5 per cent level. T-H° and T-V° did not change significantly. Different directional and magnitude changes of QRS and T-vectors were confirmed in a

smaller number of subjects using cubic and orthogonal lead systems and oscilloscopic SVEC recording. The vectorial changes, particularly in deep inspiration, cannot be due to positional changes alone, and probably reveal vagal effects on ventricular activation or repolarization. In 25 cardiac patients, the respiratory vectorial changes were frequently very different from the typical normal changes and were independent of the type of pathology.

Electric Correction of Direct Velocity to Very Low Frequency Acceleration Ballistocardiogram

DeWitt H. Smith, Princeton, N. J., and Harold W. Lewis, Madison, Wis.

Ballistocardiograms rich in details of the forces of body recoil from heart action are obtained with a light (6½ lb.) platform with 0.1 c.p.s. frequency, sensed in acceleration. However, the instrumentation is expensive. Direct Dock records are cheap, but the spring and damping of supporting tissues distort and suppress information. By using analog computer type circuitry, the effects of supporting spring and damping may be removed, yielding an acceleration record similar to very low frequency ballistocardiograms. Published tracings of this sort obtained by Talbot and by Tobin show lack of detail.

Our analog circuit is simpler. It assumes the body is a simple oscillator, and takes advantage of the similarity of the equation of motion for partially damped oscillation,

$$M\frac{d^2x}{dt^2} + K\frac{dx}{dt} + \omega^2 x = f(t)$$

and the equation of voltage drop across an inductance-resistance-capacitance circuit,

$$V(t) = L\frac{d^2Q}{dt^2} + R\frac{dQ}{dt} + \frac{Q}{C},$$

(where Q is the capacitor charge at any instant). With suitable values for capacitance and resistance, derived from an impressed oscillation,

$$\left(C = \frac{1}{\omega^2 L} \text{ and } R = kL\right)$$

effects of spring and damping are eliminated.

Input information for the circuit is from electromagnetic Dock pick-up (capacitors removed). Balanced transistor amplifier has necessary high internal resistance. The output is acceleration. Tracings obtained show details seen in 0.1 c.p.s. acceleration ballistocardiograms, but some aspects of tracings, notably width of J, depth of K, and the slant of late systole, are at times different.

A check of method is to put partially damped oscillation from an impulse impressed on the body through the circuit. This should yield trace showing what was impressed, but not the after-oscillation. Actual tracings under these circumstances show additional notches related to deviation of body from a simple oscillator. Somewhat low natural frequency of the Dock Instrument on the shins is a distortion source.

This type of correcting circuit yields records of good detail which differ somewhat from 0.1 c.p.s. tracings. The instrumentation is inexpensive and simple.

Nitroglycerin: Its Effect on the Coronary Circulation and Myocardial Metabolism in Man

Morris H. Smith and Richard Gorlin, Portsmouth, Va.

Studies in the past have indicated that nitroglycerin increases coronary blood flow along with a simultaneous reduction in systemic arterial pressure. There has been however, no measurement of myocardial oxygen consumption following nitroglycerin in relation to cardiac work, rate, and efficiency. Following coronary sinus catheterization, the nitrous oxide technic was utilized to measure coronary flow in 15 patients with systolic murmurs or only mild heart disease. Nearly simultaneous studies of cardiac output (Fick or indicator dilution method), systemic arterial pressures, pulmonary wedge and right atrial pressures, heart rate, coronary flow, and oxygen consumption/100 Gm. of muscle per minute were measured before and during sublingual administration of 0.6 mg. nitroglycerin.

A direct linear relationship has been found between myocardial oxygen consumption per systolic second and cardiac work in Kg. M./min., i.e., oxygen cost for the same work increases directly with heart rate and duration of systolic tension per minute. Nitroglycerin resulted not only in increased coronary blood flow, but also apparently increased myocardial oxygen consumption in 14 of 15 patients. The increase in oxygen consumption was out of proportion to the work done; the points lay to the right of the normal curve; and calculated cardiac efficiency decreased. Other measurements have shown a decrease in diastolic filling pressure of both ventricles and an inconstant change in radiographic heart size.

These studies would suggest that coronary flow was increased in response to myocardial metabolic alterations and not necessarily to simple coronary arteriolar vasodilatation. The possibility that nitroglycerin may result in a preferential shunt of left ventricular venous blood via the thebesian veins instead of coronary sinus cannot be ruled out by our observations. The implications of these findings in angina pectoris and in paradoxical responses to nitroglycerin will be discussed.

Heart Failure from Hypoventilation Associated with Obesity: Report of Two Cases with Physiologic Studies

Ralph E. Smith, Minneapolis, Minn., Wayne L. Hoseth, Minneapolis, Minn., James L. Brown, Minneapolis, Minn., and Mary E. Dempsey, St. Paul, Minn.*

Two short, obese patients with the congestive failure syndrome were studied. Both demonstrated cyanosis, suffused faces, and clubbing in addition to the usual evidences of the congestive syndrome.

Shunting either from an intracardiac defect or pulmonary arteriovenous fistulas was excluded by means of a dye injection technic. Alveolocapillary block was excluded by diffusion studies in both patients and in 1 by a normal lung biopsy.

Alveolar hypoventilation existed in both patients; this resulted in arterial hypoxemia (pO_2 37 and 66 mm. Hg) and hypercapnia (pCO_2 66 and 51 mm. Hg). Although 1 patient had a high minute ventilatory volume (12 L./min.), tachypnea was present with a low tidal volume (300 ml.). Marked restrictive ventilatory defects without evidence of an obstructive component were shown. The vital capacities and 1 sec. exhalation percentages were 1100 ml. with 100 per cent and 2450 ml. with 84 per cent, respectively. Both patients showed minimally defective perfusion-ventilation relationships with some perfusion of blood through nonventilated lungs resulting in alveoloarterial oxygen gradients of 18 and 16 mm. Hg with ambient air.

Both patients were shown to have pulmonary hypertension (90/? and 37/19 mm. Hg). At the time of study neither had a low cardiac output (6.0 and 7.2 L./min.). Both had electrocardiographic evidences of right ventricular hypertrophy and roentgen evidences of right ventricular hypertrophy and dilatation.

These patients are thought to represent the advanced stage of this recently described cardiopulmonary syndrome; since it is a potentially reversible entity, this etiologic variety of heart failure is important and deserves emphasis in clinical cardiology.

Interrelationships Between Dose, Serum Concentration and Toxicity in the Treatment of Atrial Fibrillation with Quinidine

Maurice Sokolow and Robert E. Ball, San Francisco, Calif.

Rational therapeutics has usually been fostered by determination of the concentration of the therapeutic agent in the blood. Quinidine can be measured fairly simply by its fluorescence in acid media. Observations will be presented to relate the dose of quinidine, the concentration of quinidine in the blood, and the therapeutic and toxic effects of the drug.

The average serum concentration in a group of patients rises with increasing doses of quinidine, but individuals vary considerably. A daily dose of 3 Gm. of quinidine, for example, may result in a fivefold variation in serum concentration in different patients. Myocardial toxicity is correlated with serum levels rather than with the individual dose of quinidine, is uncommon with serum concentrations less than 6 μg./ml., and becomes progressively greater as the concentration rises above this figure. Toxicity severe enough to require cessation of the drug rises from 1 per cent for levels under 6 μg./ml. to 8 per cent, 16 per cent, 25 per cent and 38 per cent for levels of 7, 8, 9 and 10 μg./ml., respectively.

The factors influencing successful conversion of chronic atrial fibrillation will be discussed in the light of our experience with 215 attempts at conversion. The following factors decreased the likelihood of conversion: mitral insufficiency, atrial fibrillation of more than a year's duration, and cardiac failure. Cases of nonrheumatic heart disease of short duration or uncomplicated mitral stenosis were successfully converted in at least 85 per cent of the patients.

Ninety per cent of all cases of chronic atrial fibrillation who convert to sinus rhythm do so below the level of 10 μg./ml. The decision as to whether to pursue the attempted conversion when 3 Gm. of quinidine has been given per day, or when the serum level reaches 8 to 10 μg./ml., requires knowledge of the increasing toxicity and decreasing likelihood of conversion as this level and dose is surpassed.

Angiocardiographic Diagnosis of Cardiac Septal Defects with Left-to-Right Flow

Louis A. Soloff and Jacob Zatuchni, Philadelphia, Pa.

Although the diagnosis of an atrial or ventricular septal defect can be made with a fair degree of accuracy on clinical grounds alone, important differences in surgical approach for either defect or other lesions which may mimic them make objective verification mandatory. Such verification is usually but not always supplied by cardiac catheterization. Angiocardiography has been largely ignored in attempts to demonstrate septal defects with left-to-right flow because of the prevailing belief that this technic is incapable of demonstrating such shunts. This paper describes the pathognomonic angiocardiographic patterns of atrial and ventricular septal defects with left-to-right flow.

In ventricular septal defects with left-to-right flow, the right heart and intracardiac circulation times are short in contrast to the long opacification times of the left ventricle, pulmonary artery, and aorta. Such findings are in marked contrast to those seen in heart failure and should alert one to the possibility of a ventricular shunt. In the lateral

projection, the pathognomonic pattern is seen. This consists of reopacification of the outflow tract of the right ventricle contiguous to the opacified left ventricle. Because of this recirculation, opacification time of the outflow tract of the right ventricle is likewise prolonged.

In atrial septal defect of the ostium secundum type with left-to-right flow, the dorsal border of the right atrium, which is sharply defined in the normal, is hazy or even irregularly absent because of dilution of contrast substance by nonopacified blood from the left atrium. Furthermore, at least under the conditions of angiocardiography, a small right-to-left shunt is also present. Partial opacification of the left atrium is, therefore, seen almost immediately after opacification of the right atrium. This further adds to the indefinitiveness of the dorsal border of the right atrium. Later, after opacification in the right atrium diminishes or disappears, reopacification occurs due to entrance of opacified blood from the left atrium.

In atrial septal defect of the ostium primum type with left-to-right flow, similar reopacification of the right atrium occurs. In addition, there is poor definition of the inferior portion of the dorsal border of the right atrium and intense opacification of the left ventricle immediately after opacification of the right atrium.

All 3 anomalies are associated with varying degrees of enlargement of the pulmonary artery and its branches.

The technic of angiocardiography is also helpful in uncovering associated lesions, such as anomalous veins, and in estimating the functional status of the heart.

Relationship of Left Atrial Volume to Pulmonary Artery and Wedge Pressures in Individuals with Mitral Stenosis

Louis A. Soloff and Jacob Zatuchni, Philadelphia, Pa.

Enlargement of the left atrium is a constant and characteristic finding in mitral stenosis. The degree of left atrial enlargement may vary considerably from patient to patient. Both the presence and degree of left atrial enlargement may be due to 1 or more factors, such as left intra-atrial pressure, intrinsic left atrial disease, or hypervolemia. This study attempts to determine the significance of left intra-atrial pressure, as reflected in the pulmonary artery and wedge pressures, in the production of the abnormal and variable volume of the left atrium in mitral stenosis.

Twenty consecutive unoperated individuals, 25 to 60 years old, with isolated mitral stenosis, were studied by the technics of venous cardiac catheterization and simultaneous biplane stereoscopic angiocardiography.

The method of defining the left atrial volume has been previously described (Circulation **13:** 334, 1956). The left atrial volume varied from 270 ml. to 918 ml. The mean pulmonary artery pressure varied from 10 to 72 mm. Hg and the mean pulmonary wedge pressure from 9 to 34 mm. Hg.

Statistical analysis failed to reveal any significant relationship of the volume of the left atrium to either the mean pulmonary artery pressure ($r = 0.087$, $p > 0.70$) or the mean pulmonary wedge pressure ($r = -0.023$, $p > 0.90$); nor was any significant relationship found, in these or in 18 additional cases subsequently studied, between any of these parameters and either the age of the patient or the known duration of the rheumatic state or of heart disease. Any relationship present between these parameters is obscured by more potent factors.

A Tentative Classification of Individuals with Mitral Stenosis as a Guide to Therapy

Louis A. Soloff and Jacob Zatuchni, Philadelphia, Pa.

Cardiac catheterization and angiocardiography were done in 41 individuals with mitral stenosis and shortness of breath. Findings, given below, permitted separation into groups valuable in predicting short term effects of specific, adequate therapy. All had left atrial enlargement and prolongation of left atrial time.

Group 1. Normal intracardiac circulation time (6.3 sec. or less) and normal right heart time (5.6 sec. or less). 1. Normal pulmonary artery pressure (13 mm. Hg mean or less), normal pulmonary artery wedge pressure (12 mm. Hg mean or less). These individuals have no indication for therapy to improve ventricular function or to decrease pulmonary vascular pressures. 2. Elevated pulmonary artery pressure (18 mm. Hg mean), and normal pulmonary artery wedge pressure (11 mm. Hg mean). These individuals have no indication for mitral valvotomy. 3. Elevated pulmonary artery pressure (25–34 mm. Hg mean), and elevated pulmonary artery wedge pressure (19–24 mm. Hg mean). These individuals have no indication for medical therapy to improve ventricular function. There is definite indication for mitral valvotomy to decrease pulmonary vascular pressures. Mitral valvotomy reduces the pulmonary vascular pressures and normalizes heart rate.

Group 2. Prolonged intracardiac circulation time (7.7–9.1 sec.) and normal right heart time: 1. Normal pulmonary artery and wedge pressures (none found). 2. Elevated pulmonary artery and normal wedge pressures (none found). 3. Elevated pulmonary artery pressure (26–57 mm. Hg mean), and elevated pulmonary artery wedge pressure (18–30 mm. Hg mean). Ventricular dysfunction due to an antecedent precipitating event may be present. Therapy directed against precipitating

vent may shorten circulation time and decrease ut not normalize pressures. Mitral valvotomy can urther reduce but not normalize pressures, shorten irculation time, and normalize cardiac rate.

Group 3. Prolonged intracardiac circulation time (7.7–18.2 sec.) and prolonged right heart time (7.0–19.6 sec.). 1. Normal pulmonary artery and wedge pressures (none found). 2. Elevated pulmonary artery pressure (20–26 mm. Hg mean) and normal pulmonary artery wedge pressure (10–12 mm. Hg mean). These individuals have no indication for mitral valvotomy but require intensive medical therapy for ventricular dysfunction. 3. Elevated pulmonary artery pressure (26–72 mm. Hg mean) and elevated pulmonary artery wedge pressure (14–34 mm. Hg mean). This subgroup, commonest in our series, has strong indication for medical therapy which may shorten circulation times and decrease but not normalize pulmonary vascular pressures. Mitral valvotomy can further reduce pulmonary vascular pressures and shorten circulation times. Its effectiveness diminishes, and its risk increases, the longer the circulation times and the lower the pulmonary vascular pressures. Indeed, when the right heart time exceeds long intracardiac circulation time, mitral valvotomy may prolong circulation times and increase cardiac volume.

Finally, for all groups, the larger the left atrial volume, the less effective is mitral valvotomy in decreasing pulmonary vascular pressures.

Television and High Speed Motion Picture Photography for Heart Catheterization and Selective Angiocardiography

F. Mason Sones, Jr., Cleveland, Ohio.

The practical application of television and high-speed motion picture photography, using a fluoroscopic image amplifier, for the solution of diagnostic problems in congenital heart disease will be presented.

Conventional heart catheterization and angiocardiographic technics have been modified to permit pressure measurements, recognition of abnormal shunts, and the specific visualization of anatomic lesions by selective angiocardiograms in a single stage procedure.

A simple television camera, weighing only 6 pounds, is used to permit viewing of the "amplified" fluoroscopic image on 1 or more television receivers connected to the camera in a closed circuit. This allows the team to work in a well-lighted room, and permits simultaneous observation of the field under study by any number of viewers. X-ray exposure required for fluoroscopy is reduced to 30–40 per cent (1.0 to 2.0 ma) of that required for conventional fluoroscopy.

Selection of the most appropriate sites for the injection of contrast material through the catheter for angiocardiography in each individual was determined by preliminary pressure measurements, blood oxygen determinations, and exploration of the heart chambers with the catheter. From 1 to 3 injections of 0.3 ml. of contrast material per pound of body weight were made at individually selected points during each study.

Motion pictures of each injection were made on 35 mm. film at 50 to 64 exposures/sec., by substituting a motion picture camera for the television camera at the time of injections. These may be studied in "slow motion" during projection at 16 frames/sec., or singly as individual photographs. One hundred twenty patients from 8 days to 54 years of age have been studied by this technic. The left heart has been entered by way of an interatrial communication and directly opacified in 69 patients (57 per cent). The specific solution of representative problems will be demonstrated by projection of a short 16 mm. film.

Surgical Applications of Direct Blood Flow Measurements

Merrill P. Spencer, Alberto Flores, Frank R. Johnston, Richard T. Myers, Fredrick W. Glass, and Adam B. Denison, Winston-Salem, N. C.

Fifty-seven blood flow measurements have been made during a variety of surgical procedures in order to explore the possibilities of the noncannulating square-wave electromagnetic flowmeter, surgical probe type. (Methods in Medical Research, Year Book Publishers, Inc., Chicago, 1956. In press.) The blood vessels studied have been the thoracic and abdominal aortas; renal, iliac, femoral, brachial and carotid arteries; the renal and portal veins and the pulmonary artery. The surgical procedures include herniorrhaphy, saphenous vein ligation and stripping, pyelolithotomy, nephrectomy mastectomy, thyroidectomy, carotid sinus exploration, removal of cervical nodes and tumors, arteriograms, abdominal hysterectomy, abdominoperineal resection, arterial grafts, excision of aortic aneurysms and replacement with grafts, thromboendarterectomy, lumbar sympathectomy, coarctation, patent ductus and mitral valvulotomy. Anesthetic agents have included local procaine, pentothal, ether, ethylene, cyclopropane and nitrous oxide.

The most striking over-all observation has been the profound reduction in blood flow of a peripheral artery when surgery is performed near it. Isolation of peripheral arteries such as femoral, iliac, renal, brachial or carotid unless done with great care results in extremely small flow.

The surgical applications fall into 4 main categories: (1) Evaluation of therapeutic procedures, (2) improvement of diagnostic procedures, (3) monitoring of patients' circulatory status, and (4) investigation of academic concepts.

Experience has frequently demonstrated the arterial pressure to be a poor index of blood flow.

Flow is a physiologic parameter often of greater importance to the surgeon than is pressure, though the latter has been used more because an accurate method for its determination has long been available. The first practical noncannulating meter, the square-wave electromagnetic meter, has only recently become available.

Epidemiologic Analysis of Vital Statistics on the Cardiovascular-Renal Diseases in Chicago

Jeremiah Stamler† and Yolanda F. Hall, Chicago, Ill.

In an initial report on this long-term epidemiologic investigation (Circulation **12:** 497, 1955) findings were summarized demonstrating apparent differences among various age-sex-race-occupation-income groups in 1953 Chicago mortality rates due to the major cardiovascular-renal (CVR) diseases, particularly arteriosclerotic and hypertensive heart diseases (A.H.T. and H.H.D.). In view of multiple sources of possible error in CVR vital statistics, these apparent trends required validation in further studies. Towards this end, the analysis was first extended to the 1951 deaths in the 25–64 age range.

White females consistently showed a markedly lower death rate for the following categories: all causes, CVR diseases, CV diseases, heart diseases, arteriosclerotic and degenerative heart diseases (A. and D.H.D.), other heart diseases, generalized arteriosclerosis. In the Negro population, this sex difference was much less prominent.

No gross sex differences in death rates were noted for another group among the CVR diseases, i.e., intracranial lesions of vascular origin, H.H.D., the nephritides. Death rates for these diseases were markedly higher in Negroes than in whites.

A comparison was also undertaken of the IBM-card-coded single cause of death, the multiple causes reported on the death certificate, and supplementary data obtained via query to physician. Preliminary findings indicate a significant under-estimation in vital statistics of diabetes and H.H.D. present in cases dying with coronary or cerebrovascular disease.

In the categories A. and D.H.D., and Other Heart Disease, coroner's cases (unattended deaths) constituted a significant percentage of total cases, particularly for Negro deaths.

Marked differences were noted between Negro and white deaths in relative frequency of cases coded to "Other Myocardial Degeneration." Autopsy data suggest that in terms of etiologic processes this is preponderately an artificial "waste-basket" category. Among whites, many of these cases are in fact A.H.D.; among Negroes, H.H.D. Critical re-evaluation of this category, of coroner's cases, and of single-cause coding is essential for delineating the epidemiology of the CVR diseases.

Study of Methods for Improving Records Secured from High-Frequency Ballistocardiograms

Isaac Starr and Edward W. Bixby, Jr., Philadelphia, Pa.

While the high-frequency table method of securing ballistocardiograms has advantages of simplicity, durability and ease of calibration, it has been properly criticized because the technic in common use failed to abolish movement between subject and table top. We have also found that movement between table frame and floor is a source of error.

After the second error has been corrected, and when the subject is tightly fixed to the table top, the records secured in healthy subjects seem practically identical in contour to those secured from an aperiodic or very low-frequency table when acceleration is recorded. This confirms a prediction of von Wittern.

Clinical and Laboratory Experiences with the Ergonovine Stress Test

Isidore Stein and Joseph Weinstein, Brooklyn, N. Y.

Ergonovine maleate, 0.1 to 0.4 mg., was administered intravenously as a test for coronary insufficiency in 149 patients with effort angina but a normal resting electrocardiogram, and was given similarly to 114 controls (normal subjects and patients with chest pain other than angina). The test was negative in all of the latter group. In the patients with effort angina the ergonovine test was positive in 122 (81 per cent) as shown by prompt appearance of chest pain and/or electrocardiographic changes (depression of S-T segment and/or inversion of T wave). In 112 of the patients with a positive test, both electrocardiographic changes and chest pain occurred together, 6 had chest pain alone, and 4 had electrocardiographic changes without pain. Changes in the blood pressure and pulse rate after ergonovine were minimal.

Ergonovine-induced pain could be prevented, reduced or relieved by brief application of a rapidly cooling volatile spray (ethylchloride or halohydrocarbon mixture) to reference zones of cardiac pain, or less consistently by similar application to remote areas. Spraying, however, did not prevent electrocardiographic changes characteristic of coronary insufficiency. Ergonovine plus spray with a volatile coolant offers a useful test for coronary insufficiency which may: (1) be productive of minimal pain; (2) which does not cause tachycardia which may confuse the electrocardiographic interpretation; (3) which can be done on patients who for reasons other than cardiac cannot exercise; and (4) in which electrocardiographic changes may be quickly reversed to normal by nitroglycerin.

Ergonovine tests were similarly carried out on rabbits kept on stock and cholesterol diets. Rabbits on the diets for 11 weeks or less gave negative

responses to ergonovine, while rabbits maintained on the cholesterol diet for 20 to 22 weeks all showed positive responses (significant depression of the S-T segment following ergonovine). When sacrificed, controls as well as animals kept on the cholesterol diet for the shorter period had no atheromatous involvement of the coronary arteries. On the other hand, all rabbits with positive tests showed occlusive atherosclerosis of the smaller coronary arteries with areas of myocardial damage.

Evidence for the Existence of Endotoxin in Group A Streptococcal Lysates

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Disruption of group A β-hemolytic streptococcal cells with the aid of a Mickle disintegrator, followed by high-speed centrifugation of the lysate, yields a supernatant solution which produces, on injection into rabbits, effects apparently identical with those produced by gram-negative bacterial endotoxins. These effects include the local and generalized Schwartzman phenomena: fever, leucopenia, prostration and death (with large doses). Tolerance to the pyrogenic effect occurs upon repeated intravenous injection, as in the case of endotoxins, and this tolerance can be reversed by the administration of reticuloendothelial "blockading" agents. Modifications of the action of the lysates can be obtained with cortisone and epinephrine. The lysates appear, on the basis of skin reactions and pyrogenicity, to contain relatively small amounts of endotoxin as compared with lysates or extracts of gram-negative bacteria. The nature of the active material is under study.

Effect of Hypopotassemia and Certain Other Factors on the Amplitude of the U Wave in the Electrocardiogram

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It has been found previously that an increase of the U wave in the electrocardiogram is the most important single diagnostic sign of hypopotassemia. However, a comparable increase may be caused by factors other than hypopotassemia. Independent effects of some of these factors on the amplitude of the U wave were studied in 278 electrocardiograms of persons without, and 42 persons with, hypopotassemia. This report considers only factors which significantly increase the amplitude of the U wave.

In persons without hypopotassemia, bradycardia was found to be the most important factor leading to an increase of U wave amplitude; at heart rates slower than 50/min., the average U wave was 110 per cent greater than at heart rates of 76 to 94/min., other factors being equal.

Factors increasing QRS amplitude also increase the U wave amplitude; in the electrocardiograms in which QRS amplitude exceeded 2.5 mv., the average U wave was 73 per cent greater than in those in which QRS amplitude ranged from 0.5 to 1.5 mv., other factors being equal.

The average amplitude of the U wave in persons receiving digitalis therapy was 70 per cent greater than in those not receiving digitalis, other factors being equal.

The absolute amplitude of the U wave in patients with plasma potassium concentrations of 2.0 to 3.5 mEq./L. was frequently smaller than in persons without hypopotassemia who had bradycardia and high QRS amplitude. However, when the above factors were considered, the U wave in all patients with hypopotassemia was 50 to 750 per cent greater than in corresponding groups of persons without hypopotassemia. The magnitude of this increase of U wave amplitude was found to be proportional to the deviation of plasma potassium from normal. The heart rate and amplitude of QRS must therefore always be considered in evaluating the effect of hypopotassemia on the U wave. Possible mechanisms of action of the factors studied will be discussed.

Prevalence of Diseases of the Heart in an Adult Urban Population as Estimated by Medical Examination of a Probability Sample

Joseph Tauber and Donovan J. Thompson, Pittsburgh, Pa.

This paper reports the findings of a recently completed study in Pittsburgh, Pa., which had as 1 of its objectives the estimation of the prevalence of diseases of the heart in a general population group. A probability sample of 721 persons 15 years of age and over were invited to visit a clinic operated by 1 of us (J. T.) for a thorough examination. The examination procedure consisted of a complete medical history, physical examination, 14″ x 17″ PA and, where indicated, an oblique roentgenogram, 12 lead ECG, blood analysis and urinalysis. The findings of this examination for each of the 386 persons accepting the invitation were reviewed by a group of 11 consultants in cardiology. This group re-examined 161 of these persons, some repeatedly, before the ultimate heart disease classification of each person was determined.

The estimate from this sample for the prevalence of heart disease in the study area (using the definitions of the New York Heart Association) is approximately 14 per cent. The prevalence among females is almost twice that among the males, and a large age differential exists for both sexes. Of all cases of heart disease only 7 per cent fall in therapeutic class A, while cases requiring severe restriction of normal activity (therapeutic class D and E combined) constitute 6 per cent of all cases. Rheumatic heart disease was found most prevlaent in the age group 15 to 44, while arteriosclerotic and hypertensive heart disease dominates in the older age

group. Among the males arteriosclerotic heart disease is the most prevalent.

The generally higher prevalence than previously available estimates, the sex differential, and the relative frequency of various types of heart disease which differs from that observed in some hospitals and cardiac clinics, if accurately estimated from this investigation, furnish interesting grounds for speculation.

Relationship Between Ballistocardiographic Characteristics in Groups of Males Age Twenty to Sixty with Different Characteristics

Henry L. Taylor, Minneapolis, Minn., Alfonso del Vecchio, Milan, Italy, and Ancel Keys, Minneapolis, Minn.

High frequency (Starr-type) ballistocardiograms (BCG) were recorded from 671 clinically healthy men: 493 Minnesota men (185 business men, 156 clerks, 152 railroad switchmen), and 178 men in Italy (93 policemen and firemen in Cagliari, 85 firemen in Naples). Physical examinations and electrocardiograms established the clinical health. Since no significant difference was found in the BCG characteristics (pattern abnormality or IJ amplitude) between men in Cagliari and Naples, these men were combined. In the decade 40 to 49 years, the percentage of abnormal records found was clerks 16 per cent (N = 37), switchmen 15 per cent (N = 41), and Italians 20 per cent (N = 50). In the decade 50 to 59, switchmen and clerks 37 per cent (N = 71), businessmen 42 per cent (N = 185), and Italians 40 per cent (N = 37). IJ amplitudes of records with normal patterns were measured and regression equations with age and height were calculated. No significant differences were found in the IJ amplitude between switchmen and clerks, or between Americans and Italians. Serum cholesterol concentrations in these Italians were significantly less than in the American groups. It is generally agreed that there is much less ischemic heart disease among men in southern Italy than among Americans. Further, it has been suggested that physically active individuals have less ischemic heart disease than sedentary individuals. The data presented here are not consistent with the hypothesis that the age trend in BCG characteristics is dependent on developing ischemic heart disease. It is concluded that the ballistocardiograph employed here is not a useful instrument for investigation of the epidemiology of ischemic heart disease.

Surgical Approaches to the Problem of Myocardial Ischemia

Alan P. Thal, Fletcher A. Miller, and Christian N. Barnard, Minneapolis, Minn.

As Zoll has shown, the most severe lesion of coronary arteriosclerosis affects the first 2 centimeters of the major branches. Indeed, occlusive disease may be localized to a short segment of a main branch. On the other hand, more commonly, there are multiple lesions in several branches. Where the lesion is focal, direct anastomosis of an extracardiac vessel to the coronary artery distal to the point of occlusion might be feasible. By using a perfusion system with oxygenated blood it is possible to perform this procedure over as long as a 30 min. period without encountering ventricular fibrillation. When the perfusion system was not used, ventricular fibrillation occurred within 10 min. in almost 100 per cent of the dogs after occlusion of the circumflex artery. Initially, flows through the divided circumflex of 30 ml. of blood/min. were used. Later it became evident that lesser quantities were needed and equally good results were obtained when as little as 10 ml./min. was perfused. Follow-up studies of 17 dogs with this type of anastomosis revealed a widely patent, functioning anastomosis in 7, 6 months after operation.

A technic for implanting a capillary bed into the myocardium will be described. In this case, intercostal muscle bundles containing artery, vein, and nerve were used, and threaded into the myocardium. Follow-up studies in these animals reveal a formation of extensive capillary anastomoses between the embedded intercostal vessels and the myocardium. Scar reaction to this procedure is minimal, and follow-up study at 3 months shows no evidence of atrophy of the intercostal muscle bundle.

A technic for obtaining detailed coronary arteriograms using the image intensifier will also be presented.

Mode of Action of the Lipopolysaccharide Endotoxin of Gram Negative Bacteria

Lewis Thomas, Benjamin W. Zweifach,† and Arnold Nagler, New York, N. Y.

The vascular lesions produced by endotoxins, in the rabbit, include fibrinoid necrosis of the coronary and pulmonary arteries, deposits of fibrinoid in the mitral and aortic valves, and the occlusion by fibrinoid of the glomerular capillaries and sinusoids of the liver and spleen. The fibrinoid material is derived from precipitation of fibrinogen, presumably by combination with an acid mucopolysaccharide.

The systemic reactions to endotoxin include fever, peripheral arteriolar constriction and vasomotion, the appearance of heparin-precipitable fibrinogen in plasma, hyperglycemia, and elevated blood lactic acid, depletion of liver glycogen, and terminally vascular dilatation and shock.

Some of the effects of endotoxin can be accounted for by altered reactivity to adrenaline or noradrenaline in the vessels of the intoxicated animal. In the rabbit, endotoxin produces a local direct effect in the vessels of the skin which renders the

issue vulnerable to extensive necrosis when adrenaline is injected. Hemorrhagic necrosis can be produced by 2–10 μg. of adrenaline in the presence of 5 μg. of endotoxin.

In the rat, the vessels of the mesocaecum show 2 types of altered reactivity to adrenaline following an intravenous injection of endotoxin. With 50–250 μg. of endotoxin, there is an increase in reactivity by as much as 1000-fold. With 500–2000 μg., the vessels become hyporeactive and show marked dilatation and stasis of blood flow. The reactions involve venules as well as arterioles and are accompanied by local petechial hemorrhages.

In the isolated, perfused rabbit ear, comparable alterations have been demonstrated. Perfusion of endotoxin by itself causes no change in blood flow. After perfusion of 0.5 μg./ml., the vessels become excessively reactive to adrenaline. After doses of 35–70 μg./ml. of endotoxin, adrenaline produces extreme vasodilation. The latter reaction does not occur in the absence of potassium in the perfusing fluid. The mechanism whereby cortisone and related agents alters the vascular responses to endotoxin are under investigation.

The results indicate a direct action of endotoxin on blood vessels, leading to altered reactivity to adrenaline. This change in reactivity may be the primary event which accounts for many of the physiologic effects of endotoxin, including ischemic tissue necrosis, shock, and death.

Experimental Arteriosclerosis due to Combinations of Hypercholesterolemia and Hypervitaminosis D

Richard E. Trueheart, Marjorie Stumpe, and George M. Hass, Chicago, Ill.

Two forms of arteriosclerosis were produced in 2 different series of rabbits. One form was produced by dietary hypercholesterolemia. The other was produced by injections of irradiated ergosterol. The hypercholesterolemic disease was characterized principally by atheromatosis in the intima of certain arterial systems with secondary, atheromatous changes in the media of the same arterial systems. The arteriosclerosis produced by excessive doses of irradiated ergosterol was characterized primarily by degenerative-calcific changes in the media of certain arterial systems with secondary fibroelastic proliferative reactions of the intima of the same systems in the neighborhood of medial disease. Combinations of these 2 methods of producing experimental vascular disease were used in a third group of animals. These studies indicated that the nature of the fundamental lesion, so characteristic of each individual disease, was greatly modified by admixture of the 2 metabolic disorders. Appropriate admixtures led to several patterns of atherosclerosis which were a reflection of the rate of development, sequence, severity and duration of each of the 2 fundamental disturbances. Accumulated observations on more than 100 rabbits lend strength to the view that the experimental production of forms of arteriosclerosis, which resemble the common types found in man, involves production of basic changes in the arterial wall. The extent to which these changes favor atheromatous localization depends not only upon the nature and location of the changes in the arterial wall but also upon the composition of the plasma lipids and other still unrecognized factors. Among these unrecognized factors are those mechanisms which regulate the distribution of lesions in the 2 basic forms and the combined forms of the disease. These must vary from place to place because each part of the arterial system has a specific susceptibility or resistance to the mechanisms responsible for the development and regression of the experimental arteriosclerotic changes.

Concept of "Masquerading" Bundle-Branch Block: An Electrocardiographic-Pathologic Study

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The electrocardiographic pattern called "masquerading" bundle-branch block is characterized by left bundle-branch block pattern in the extremity leads, and right bundle-branch block pattern in the precordial leads. In 1953, Rodriguez, Anselmi and Sodi-Pallares considered this to be left bundle-branch block with infarction of interventricular septum and free walls of both ventricles. Richman and Wolff also interpreted this as left bundle-branch block with predominantly septal infarction.

We have had the opportunity of studying 4 autopsied cases with this electrocardiographic pattern, as well as with evidence of septal infarction with involvement of the free walls of the left ventricle. The hearts in these cases, including the entire conduction system, were studied by a skip-serial section technic devised by 1 of us (Lev), thus making possible for the first time an electrocardiographic-pathologic correlation in this entity.

The following pathologic findings were common to all cases: (1) incomplete, diffuse damage to both right and left bundle-branches, and (2) impairment of the blood supply to the septum with widespread damage to the septal myocardium and involvement of the free walls of the left ventricle. In only 1 case was the right ventricular free wall significantly involved.

These findings support the thesis that masquerading bundle-branch block is in reality a type of bilateral bundle-branch block associated with widespread septal damage. This is in contrast to the concept that this pattern represents left bundle-

branch block masquerading as right bundle-branch block.

Effect of Mitral Commissurotomy on Coexisting Aortic Valve Lesions

Joseph F. Uricchio, Philadelphia, Pa.

The ideal response to mitral commissurotomy includes a normal blood flow into the left ventricle unaided by a pressure rise in the left atrium, and the return of cardiac output to normal levels even under the stress of exercise.

The manner in which the heart responds to the modification of mitral obstruction when aortic valve lesions coexist and are uncorrected rarely has been brought to serious question.

This communication records 3 instances in which mitral commissurotomy was succeeded by unmistakable evidence of an increase in the severity of the aortic valve defects. The devolutionary patterns of these patients, their clinical manifestations and physiologic studies are documented in an exploration of a basic explanation.

A theoretic reconstruction of the dynamic events is based on the assumption that mitral commissurotomy augments rate of flow per unit of time into the left ventricle. Subsequent hemodynamic balance is maintained by an increased rate of flow per unit of time across the aortic valve. When aortic stenosis coexists, this is followed by a proportional rise in the pressure gradient between the left ventricle and aorta. With time the exaggerated demands on the myocardium results in a loss of contractility and failure.

Thus the surgical correction of mitral stenosis compounds the basic effect of aortic obstruction in a manner simulating an increase in the actual stenosis.

An additional mechanism, "over-stretching" of the myocardium may be involved when aortic insufficiency also is present. This results from the dual diastolic volume load accruing from the commissurotomy and the aortic lesion which may diminish the ability of the left ventricle to sustain sufficiently high intraventricular pressures for systolic ejection.

The inquiry into this problem is pertinent since in these experiences each patient died.

Pueblo's Program for Prevention of Rheumatic Fever, Including the Development of a Registry for Rheumatic Fever and all Heart Disease of Children

Wesley Van Camp and John S. Anderson, Pueblo, Colo.

The 15 physicians staffing Pueblo's Medical Society-sponsored Heart Clinic provided the nucleus for our program. The distribution by the American Heart Association of the committee report regarding Prevention of Rheumatic Fever in February, 1955, challenged these physicians to join with the Health Department, schools, and parent-teacher associations in a county-wide educational program.

In the spring of 1955 the film, "Stop Rheumatic Fever" was shown at all faculty meetings in the county with a physician present to lead a discussion afterwards. During the past school year a similar program was presented at most Parent-Teacher Association meetings in the county, with a physician commentator again present. A printed questionnaire regarding rheumatic fever, and rheumatic or other heart disease, was sent home with 19,266 school children in the county. Of the distributed questionnaires, 13,325 or 69.2 per cent were returned. Although this survey had little statistical value, it had some case-finding value, and considerable educational merit.

The most unique and difficult part of the program was the development of a Central Registry—located at the City-County Health Department—for the reporting of all cases of rheumatic fever and childhood heart disease of all types. This registry is too new to ascertain its complete usefulness, but it has been an important tool in correlating the entire program. The technical problems of developing the registry were accomplished with the help of a record analyst on loan from the U. S. Public Health Service. Encouragement, technical, professional, and financial aid from the Colorado Heart Association, the State of Colorado Department of Public Health, and the U. S. Public Health Service made Pueblo's program bigger, better, and more stimulating to all participants.

A Study of Pituitary-Adrenal Function in Families of Rheumatic Subjects

L. George Veasy and Vincent C. Kelley, Salt Lake City, Utah

Because of the well-established familial predisposition to rheumatic fever and the recent demonstrations of abnormal adrenal function in rheumatic subjects, this study was undertaken to determine whether any abnormality in hormonal pattern could be demonstrated in members of the families of rheumatic subjects. This is a preliminary report concerning the early findings in this study. A total of 285 members of 47 families have been studied to date. No individuals were included who had any evidence of rheumatic activity by history, physical examination, or laboratory criteria.

Blood was withdrawn for determination of circulating concentrations of 17-hydroxycorticosteroids by the method of Nelson and Samuels, corticosterone and 17-hydroxycorticosterone by the

method of Sweat, and ACTH by the assay of Sydnor and Sayers.

The individuals in the study were divided into the following groups: 1. Parents with a positive history of rheumatic fever. 2. Parents with a negative history of rheumatic fever. 3. Siblings with a positive history of rheumatic fever. 4. Siblings with a negative history of rheumatic fever.

The mean 17-hydroxycorticosteroid levels were similar in all groups (approximately 7 μg. per cent) and were significantly lower than normal (12 μg. per cent).

The corticosterone levels in all groups were significantly higher than normal. In both groups of parents the mean levels were the same. However, among the siblings, the group with a positive history had higher levels than the group who gave no history of rheumatic fever.

ACTH determinations were done on 66 individuals. In our experience no normal child has been shown to have any detectable ACTH level. Among the siblings, however, approximately 25 per cent (11 of 41) did have measurable ACTH in the blood.

Evidence which has been obtained that members of rheumatic families may produce an abnormal adrenal cortical hormone, will be discussed.

Effect of Systemic Blood Pressure on the Coronary Circulation

Lauro B. de Vera, Los Angeles, Calif., Eliot Corday, Beverly Hills, Calif., and Herbert Gold, Beverly Hills, Calif.

While there is a great need for a good collateral circulation in acute coronary thrombosis, a satisfactory means of improving it at such a stage is yet to be devised. Vigorous management of shock, such as with norepinephrine, however, has been reported to reduce the mortality due to acute myocardial infarction with hypotension. Inasmuch as the mechanism of action of such a vasopressor on the collateral coronary circulation is not clearly understood, the authors have therefore studied the effect of systemic blood pressure on the same isolated circulatory system.

Introducing a new method for evaluating the collateral coronary circulation in the dog's beating heart, the anterior descending artery was cannulated above and below a ligature placed near its origin, and the antegrade and retrograde (collateral) flows were measured simultaneously for 1 min. In 69 dogs, the average retrograde flow was 3.07 ml., the average antegrade flow 30.68 ml., and the average retrograde-antegrade flow ratio, 10 per cent.

In 30 dogs with hypotension, produced either by the coronary ligation itself or by bleeding, the effect of Levophed, Vasoxyl, artificial coarctation, plasma expander, and blood were recorded. In all instances, regardless of what pressure elevating agent or method was used, the antegrade flow and, by proportion, the retrograde flow increased very significantly as the systemic blood pressure was restored to normal. In some experiments, elevation of blood pressure by 30 mm. Hg augmented the collateral flow to double its original amount. In 3 dogs, a possible coronary vasodilator action of Levophed was entertained.

The authors conclude that restoring the systemic blood pressure to normal is of physiologic importance in the treatment of acute coronary thrombosis, especially with extreme hypotension.

Problems in the Use of Different Tissue Thromboplastins in the Control of Anticoagulant Therapy

Marc Verstraete, Patricia A. Clark, and Irving S. Wright, New York, N. Y.

At present there is no standardized preparation of tissue thromboplastin available for the control of coumarin therapy. The commercial thromboplastins used are from different sources, mainly horse or rabbit brain and lung, or a combination of both. The mode of extraction for each of them may be different.

Using the same technic of prothrombin time determination (1-stage method, Link-Shapiro modification), 9 different commercial thromboplastin preparations were studied. Although many of these thromboplastins have a prothrombin time on normal plasma varying in a narrow range, there appears to be important differences between the results obtained with these thromboplastins when plasmas of patients undergoing coumarin-derivative treatment are tested. The object of the present investigation is the study of the causes of these differences. The properties and mode of action of different types of tissue thromboplastins were therefore investigated.

Brain preparations give shorter values for coumarin plasma than pure lung preparations because they appear to have a factor VII-like activity. The decrease in factor VII concentration is generally considered to be the most important change in the clotting factors during coumarin therapy. An accurate evaluation of this factor is therefore essential for the correct control of coumarin therapy.

It was also found that some of the thromboplastins tested showed a factor V-like activity.

These important differences in properties of tissue thromboplastins are at least partly responsible for the great discrepancy in reported 1-stage prothrombin times and, therefore, in the doses of coumarin derivatives used in different well-known centers to achieve adequate anticoagulant therapy.

Six Months to Six Years Experience with Eighty-Five Cases of Coronary Artery Insufficiency Treated by Internal Mammary Artery Implantation

Arthur M. Vineberg, Montreal, Canada, and James H. Walker, Charleston, W. Va.

The surgical treatment of coronary artery insufficiency by internal mammary artery implantation was first attempted at McGill University in the animal in 1945, and in man in the Royal Victoria Hospital in April 1950.

During the past 11 years much experimental evidence has been gathered to show that when an internal mammary artery is placed in the left ventricular myocardium, it grows arteriolar branches which anastomose with the vast arteriolar network lying within the ventricular myocardium.

These mammary coronary anastomoses are extensive, and through them fresh arterial blood is sent to the myocardium in sufficient quantities to relieve myocardial ischemia, caused by artificially produced coronary artery insufficiency.

Our experimental evidence has been confirmed in other centers when it is carefully repeated. Bailey and co-workers have reported blocked arteries caused by thrombosis or intimal proliferation in their experimental animals in a very high percentage of implants. Unfortunately these arteries were left in normal hearts for 6 months.

In our experimental series of many hundreds of animals, the anterior descending branch of the left circumflex has been ligated 6 weeks after implantation, thus producing a need in the new artery. Such internal mammary arteries examined 5, 6, and 7 months later have widely patent functioning lumina.

In the human suffering from severe anginal pain due to coronary artery disease, there is ischemia of the ventricular myocardium. An internal mammary artery placed in this type of muscle has little competition. The surrounding coronary arteries narrowed by disease fail to supply the myocardium with the required amount of blood. The implanted healthy internal mammary artery is needed and does not close off by intimal proliferation when examined 18 months later.

In a recent report by 1 of us (A. V.), concerning 8 human internal mammary arteries examined from 24 hours to 18 months after implantation, there was only 1 blocked artery. In none was there intimal proliferation. There were 2 cases in which the artery was examined 4 months and 18 months after surgery. Both of these patients had a widely patent internal mammary artery lying within the myocardial tunnel, giving off numerous branches to the surrounding arterioles.

In this paper the authors wish to combine their experience in the treatment of human coronary artery insufficiency, reporting a total of 85 patients, 54 of whom have been operated upon in Montreal by the senior author and 31 by the co-author in Boston and Charleston, West Virginia.

The mortality for patients with no angina at rest is between 3 and 6 per cent, whereas the mortality for patients with angina decubitus (by this we mean pain at rest without exciting cause), is very much higher and ranges between 45 to 50 per cent. Approximately 84 per cent of our patients have had 1 or more previous infarctions and 85 per cent have been unable to work at the time of operation.

In the group of patients without angina at rest, 75 per cent are pain free or have slight pain. Roughly 10 per cent have less pain. Others are not improved or died. Approximately 78 per cent of this group have returned to work and over 67 per cent are still working.

In the angina decubitus group of cases, only 21 per cent are pain free or have slight pain after the operation and 21 per cent have returned to work. The balance have either died or slowly degenerated.

There is evidence that the internal mammary artery implanted into ischemic human hearts caused by coronary artery disease, remains open in 85.8 per cent. Further, in the artery examined 18 months after implantation, not only is the artery open and branching but it shows little, if any, intimal proliferation.

The clinical results in which 75 per cent of patients with coronary artery insufficiency are relieved of anginal pain after internal mammary artery implantation, corresponds to the known mammary coronary anastomotic rate in animals and the percentage of arteries known to remain open in man.

Differential Effect of Dietary Fat and Weight Reduction on Serum Levels of β-Lipoproteins

Weldon J. Walker, Norman Weiner, and Lawrence J. Milch, San Antonio, Tex.

The effect of dietary fat intake and weight reduction on levels of the various classes of serum lipoproteins was determined in 25 human subjects. The majority of patients had proven coronary artery disease. During the first period of the study, the patients sustained an average weight loss of 21.7 pounds while on a diet in which approximately 73 per cent of total caloric intake consisted of animal fat. Following this period of weight loss the patients' weights were maintained constant while they continued to ingest this high-fat diet in increased quantities. Finally, subjects were maintained at a constant weight on a diet containing less than 50 Gm. of fat per day. Standard S_f 0–12 and S_f 20–400 classes of β-lipoproteins showed a completely dissimilar response. The serum levels of the S_f 0-12 fraction were highly influenced by dietary fat intake rising on a high-fat diet and

falling on a low-fat diet, apparently independent of weight change. In contrast the S_f 20–400 fraction was significantly lowered by negative caloric balance and weight reduction despite the ingestion of large amounts of animal fat. These changes were statistically highly significant. The S_f 12–20 class of lipoproteins showed less striking responses to weight reduction and dietary fat intake. These data lend support to the concept that body leanness and restriction of dietary fat may both be important in preventing atherosclerosis. In addition divergent responses of different classes of β-lipoproteins to various dietary and nutritional regimens may be entirely missed if only total β-lipoprotein or total cholesterol measurements are made.

Pressure Relationships Among Arteries and Large and Small Veins

John M. Wallace, Durham, N. C.

Using small catheters, pressure changes (in mm. Hg) in small hand veins, large forearm veins and the radial artery have been studied in normal subjects. In 4 subjects the 3 pressures were recorded simultaneously. In 5, artery and large vein, in 6 the 2 veins and in 2 both radial arteries were studied.

Small vein pressures pulsated, were spontaneously more active, and ranged 1–8 mm. above the large, differences being greater in the seated than recumbent position. Small vein pressures often doubled during noradrenaline infusions, and doubled or tripled in cold (up to 40 mm.), both stimuli markedly increasing pulsations; large veins changed little. Arm baths of 10 C. affected arterial pressures relatively little.

Vessel reflexes were easily observed if the arm was first congested, then occluded by a cuff at 270 mm. Coughs, respirations, Valsalva maneuvers, apprehension, pain, 10 per cent CO_2 and remote cold often caused rises of 10–15 mm. in veins, 2–6 mm. in arteries. Large vein pressures usually rose and remained above the other 2, which tended to equalize. TEAC injected intravenously distant from the occluded area abolished the responses. Similar noradrenaline injections caused slight rises in venous pressures and equivocal or no arterial changes. Local exercise markedly dropped arterial pressures, caused little change in small veins and elevated large vein pressures. Venous pressures have risen without arterial rises, but not vice versa.

Following release of an average of 8 min. of occlusion the pressures in small veins pulsated vigorously, rose above the large which then fell more rapidly. Arterial and pulse pressures were low (range 70/50) and became normal in 1–3 min.

Under certain experimental conditions the pressures in small veins vary strikingly from those in large ones. Recording pressure changes in vessels below an occluding cuff is a useful means of demonstrating reflex activity.

Results of Direct Vision Repair of Ventricular Septal Defects: Report of the First One Hundred Patients

Herbert E. Warden, Donald J. Ferguson, Richard A. DeWall, Paul Adams, Raymond C. Anderson, Richard L. Varco, and C. Walton Lillehei, Minneapolis, Minn.

Since March 26, 1954, at the University of Minnesota Hospital, more than 175 patients with intracardiac lesions have undergone direct vision repair of their defects. During the period of total cardiopulmonary by-pass necessary for these open cardiotomy procedures the patients were perfused with arterial blood provided either by the controlled cross circulation, the arterial reservoir, the biologic (dog-lung) oxygenator, or the mechanical (bubble) oxygenator technics.

These operations have been performed for acquired as well as congenital intracardiac disease. However, defects of congenital origin have been by far the most common and have included such anomalies as atrioventricularis communis, tetralogy of Fallot, and interventricular septal defects. The latter defect has been the most frequent type encountered in this entire series. Therefore this paper will be concerned solely with the presentation of the results of the open surgical treatment of the first 100 patients with interventricular septal defects.

The over-all mortality in this group of patients undergoing direct vision repair of their ventricular septal defects was 30 per cent (30). Of these 27 (27 per cent) were early and 3 (3 per cent) were late deaths in patients more than 6 weeks postoperative. When the preoperative catheterization data, the patient's age and the presence or absence of pulmonary vascular changes (as gleaned from lung biopsies), are correlated with mortality several important features become apparent. These are too numerous to describe in detail in abstract form but in essence they are: 1. In general the mortality is greatest in the infant less than 1 year of age who has a pulmonary artery pressure greater than 70 per cent of his aortic pressure. This mortality rate in patients with high pressures is less in the older age groups. 2. When the pulmonary artery-aortic pressure ratio is less than 70 per cent the outlook is much more favorable in all age groups but especially in the patients over 2 years of age in which the mortality was less than 10 per cent.

To date approximately ¼ of the surviving patients have been recatheterized and in all but 3 the intracardiac dynamics have been found within a normal range. It is expected that several more will have undergone these postoperative studies in

the coming weeks and will be available for inclusion in this presentation.

AVR—A Clue to Right Ventricular Hypertrophy

Richard H. Wasserburger and John B. Brown, Madison, Wis.

This paper was undertaken to establish electrocardiographic criteria for the diagnosis of right ventricular hypertrophy in infants and children. The first part of this investigation was designed to establish the normal patterns in the electrocardiogram in a population between the ages of 1 month and 14 years. Electrocardiograms were taken on 1,000 children without evidence of heart disease from the pediatric wards and in public schools. Criteria generally accepted as indicating right ventricular hypertrophy were critically examined. RSR′ patterns were commonly observed in the right precordial leads as were predominant R waves. An important observation in this group was that the amplitude of the late R wave in lead AVR in the presence of a vertical heart, never exceeded the amplitude of the preceding negative deflection.

The second part of the study was concerned with the finding of more reliable criteria for the electrocardiogram diagnosis of right ventricular hypertrophy. Two hundred and seven patients with congenital and acquired heart disease were selected, proved to have elevated right ventricular work indices (greater than 1.0 Kg./M.²/min.) as determined at time of cardiac catheterization. The ratio, right ventricular work index to left ventricular work index, (RVWI/LVWI) was found to correlate with observed electrocardiographic findings better than either the right ventricular work index itself, or the right ventricular pressure. This will be called the ventricular work load ratio, as it has not been previously described. Regardless of the diagnostic classification of the patient, when the ventricular work load ratio exceeded 0.67, thereby hemodynamically indicating a predominant right ventricular lesion, the following electrocardiogram criteria were present: (1) a prominent late R-wave in lead AVR in a vertically placed heart, and (2) the presence of an RSR′ pattern with a predominant R′ wave, a pure R-wave, or a qR pattern in the right precordial leads, with evidence of delayed ventricular activation time.

It is felt that lead aVr is a useful electrocardiographic lead in detecting right ventricular hypertrophy in the presence of variants of RSR′ patterns in the right precordial leads.

Unusual Postoperative Complications of Mitral Commissurotomy

Richard W. Watts, Cleveland, Ohio.

The occurrence of emboli and the postcommissurotomy syndrome have been well documented. We wish to present 3 other less common complications of commissurotomy, left phrenic palsy, depression and poor vision, and the appearance of other murmurs. These complications have been observed in a series of 80 cases since 1951.

Left phrenic palsy has occurred in 3 cases. It is due to traction of the nerve after opening the pericardium. In the first case persistent atelectasis and bronchopneumonia recurred until regeneration of the nerve occurred 3 months postoperation. In the other 2 cases there has been only a reduction in vital capacity but there has been no nerve regeneration in 46 and 7 months respectively.

Difficulty in focusing and depression of mood has occurred in 7 patients in 1 instance being accompanied by brief auditory delusions. In every case these symptoms subsided in 1 to 4 weeks. It is our belief that this is the result of brief cerebral anoxia due to mitral valve obstruction at the time of operation.

The appearance of murmurs not heard preoperatively refers to other valvular murmurs and not that of mitral insufficiency. This has occurred in 2 cases. In 1 case an aortic diastolic murmur appeared but 52 months later there is no evidence that it is dynamically significant. In the other case both systolic and diastolic aortic murmurs appeared but without apparent dynamic signifi cance 11 months later. Both cases were observed preoperatively on many occasions by several examiners, none of whom heard the aortic murmurs. Postoperatively they have done well. We believe this is due to increased cardiac output after operation permitting the propagation of murmurs of greater intensity.

Effect of A-V Nodal Blockade on Fibrillation Following Acute Coronary Arterial Occlusion

Watts R. Webb, Jackson, Miss.

The basic mechanisms of ventricular fibrillation have not as yet been clearly elucidated. It is known that the incidence of fibrillation following various methods of induction can be altered by numerous drugs, electrolytes, and hormones which may act on the myocardium itself or on the conduction system. Similarly, sympathetic nerve interruption, either by thoracic sympathectomy or at the S-A node, has been shown to protect against arrhythmias induced by such stimuli as ventriculotomy during hypothermia.

The present study concerns the incidence of ventricular fibrillation as it may be effected by factors altering, in so far as possible, only the conduction system of the ventricle itself. In mongrel dogs, the conduction bundle in the region of the A-V node has been blocked with procaine or divided surgically to produce complete A-V dissociation. Previous observations on 28 dogs demonstrated that, in this preparation, a faradic current, which

will always produce fibrillation in control animals, will only rarely produce fibrillation in the presence of an A-V nodal rhythm. If an idioventricular rhythm were produced, fibrillation never occurred following this stimulus.

This study has been extended to observations of arrhythmias following total left coronary artery occlusion which presents a maximal stimulus. In control animals, ligation of the left coronary artery at its origin produces ventricular fibrillation in a brief interval, ranging from 30 sec. to 12 min. However, after anesthetization of the A-V node, instead of fibrillating following left coronary occlusion, the ventricles gradually decrease their rate and force of contractions to virtual standstill, though diminished electric impulses may be recorded longer.

This protection of the ventricles from fibrillation by blockade of the A-V node not only has clinical implications, but suggests a basic role for the A-V node in the maintenance of ventricular fibrillation.

Relation of Embryologic Growth Rates to the Development of Congenital Malformations of the Heart

Bernice G. Wedum, Edwin D. Vaden, Richard J. Waters, and E. Clarence Rice, Washington, D. C.

Young, rapidly growing tissues, and rapidly dividing cells such as those of a malignant growth, are far more sensitive to environmental influences than older or slower growing cells. It seemed possible that this principle might operate in the production of congenital malformations of the heart, structures developing at a rapid rate being more readily affected by adverse influences with a resultant higher incidence of malformations involving these more sensitive tissues.

To test this hypothesis, growth rates were measured directly on models or serial bromides of sections of embryos 27–39 days old. The rate of growth of the spiral septum partitioning the truncus arteriosus is .016 mm./day, of the septum primum .012 mm./day, and of fusion of the proximal bulbar ridges with the crest of the ventricular septum approximately .016 mm./day.

In a group of 246 autopsy specimens of congenital malformations of the heart at Children's Hospital in Washington, there are 6 cases of truncus arteriosus communis representing an arrest of growth of the spiral septum, 12 cases of atrioventricularis communis (without associated lesion) representing an arrest of the downward growth of the septum primum, and 10 cases of ventricular septal defect (without associated lesion) representing a failure of the proximal bulbar ridges to fuse completely with the crest of the ventricular septum. The true incidence of ventricular septal defects is undoubtedly far higher; the relative incidence of truncus arteriosus and atrioventricularis communis is probably accurately represented in this autopsy series.

The partitioning of the truncus is a more rapid process than the downward growth of the septum primum and equals the rate of closure of the ventricular septum, yet a true truncus arteriosus is by far the least common of these 3 malformations. This study supports the conclusion that embryologic growth rates are not related to the production of congenital malformations of the heart.

Clinical Experience with Metaraminol in the Treatment of Shock

Max H. Weil and Wesley W. Spink, Minneapolis, Minn.

The practical value of vasopressor agents in the treatment of shock related to myocardial infarction, pulmonary embolism, bacteremia and other medical emergencies has been widely acknowledged. We have recently investigated the usefulness of metaraminol, a new synthetic sympathomimetic amine closely related to norepinephrine (Levophed). In contrast to the alarming frequency of tissue necrosis and slough that follows the use of norepinephrine, we noted that metaraminol also produces a very potent pressor effect without tissue damage at the site of injection. The undiluted drug may be administered by the intravenous, intramuscular, or subcutaneous route. This is particularly useful when fluids have to be curtailed because of renal insufficiency. Dependable and prolonged action of intramuscular and subcutaneous injections makes intermittent therapy convenient and effective.

Initial studies involved 42 patients in shock with average blood pressure of 68/57 mm. Hg. Administration of metaraminol was followed by prompt elevation of pressures to an average value of 120/76 mm. in 36 patients. The blood pressure was supported for 4 or more hours in 32 patients and 28 patients recovered from shock. Results have been at least as satisfactory as those reported for norepinephrine.

A single intravenous injection of 3–15 mg. of metaraminol was usually effective in producing a prompt elevation of the blood pressure lasting 10–25 min. In most patients the blood pressure was subsequently maintained on 3–25 mg. subcutaneously repeated every ½–2 hours. In instances of profound shock, the continuous intravenous infusion of metaraminol in equivalent dosage was preferred.

We have employed metaraminol in the therapy of more than 500 patients. The agent has proven remarkably free of toxic side effects and pressor potency did not decrease with prolonged therapy. The feasibility of intermittent subcutaneous administration was particularly apparent in patients with coronary thrombosis and in patients with bacteremia who required continuous vasopressor

support for prolonged periods often exceeding 1 week.

Essentials in the Treatment of Atrial Fibrillation: Individual and Combined Roles of Digitalis and Quinidine

Samuel A. Weisman, Los Angeles, Calif.

Too frequently, and particularly in the last few years, more and more case reports have been appearing in the literature of shock-like syndromes, convulsions and sudden deaths following the use of quinidine in the treatment of atrial fibrillation. In some series, the number of deaths was almost 10 per cent.

An uncritical reading of the aforementioned publications might leave one with the impression that the use of quinidine was hazardous. An analysis of these reports, however, discloses that the management of the cases was questionable. An overzealous effort to reach certain quinidine blood levels as quickly as possible, an insufficient knowledge of the pathophysiology of a fibrillating heart and the pharmacology of quinidine and digitalis are the principal reasons for these serious complications.

It is well established that a fibrillating heart is not a fully compensated heart; the cardiac output is diminished from 15 to 79 per cent. Quinidine is a myocardial depressant. Digitalis is a myocardial tonic. To begin treatment of atrial fibrillation with quinidine, and particularly with large, too frequent doses, means the administration of a myocardial depressant to an already embarrassed heart. This invites danger. A fibrillating heart must first be "conditioned" for the optimum effect of quinidine. This is done by first digitalizing the heart, and keeping it digitalized. By so doing, much less quinidine is needed to restore normal rhythm and the danger of its use is minimized.

In my experience of some 27 years in the treatment of over 1,000 cases of chronic atrial fibrillation, I have had but 1 death that could be attributable to the use of quinidine.

Experimental studies, the method of treatment and case reports will be presented.

Increase in Glucose Levels in Blood from Antecubital Vein During Forearm Exercise

Arnold M. Weissler, Durham, N. C.*

Simultaneous arterial and deep antecubital venous glucose levels were determined by the Somogyi titration method in 13 normal subjects and 2 patients on high carbohydrate (rice) diet during 1/sec. fist-clenching exercise. Specimens were obtained at rest and after 1, 3, 5, 7, 10, and 15 min. of exercise.

Arterial levels remained relatively constant throughout exercise, usually varying within 1.1 mg. per cent of the mean for each subject. Venous levels followed a consistent pattern. There was an initial rise averaging 5.0 mg. per cent ($\pm$1.65) at 1 min., with gradual fall thereafter to approach resting levels after 15 min. of exercise. Venous glucose levels exceeded arterial at 1 min. in 13 subjects and at 3 min. in another. In only 1 subject was a negative A-V difference not observed. The mean negative A-V difference at 1 min. was 1.9 mg. per cent with a range of 0.1 to 6.0 mg. per cent. Mean oxygen content of venous samples during exercise was 8.5 vol. per cent ($\pm$0.6 vol. per cent). Venous hematocrits by the capillary method varied no greater than 1.0 per cent throughout exercise. Glucose oxidase treatment of filtrates in 6 of the subjects indicates that the reducing substance involved in the above changes is true glucose.

The above-described arteriovenous glucose curve can be attributed in part to circulatory changes during exercise (narrowed A-V difference secondary to increased blood flow). The observed negative arteriovenous differences are outside of the methodologic error in our hands (S.D. $\pm$ 0.3 for method, $SEM_{(A\text{-}V\ Diff)} \pm 0.18$ for duplicate samples, p values <0.05 to <0.01). Since the low oxygen levels make skin flow an unlikely contaminant of the sampled blood, we believe the observed changes to represent a release of glucose from muscle cells or intercellular fluid into the venous circulation during the initial stages of local exercise.

Pulmonary Embolism: Observations with a New Experimental Approach

Stanford Wessler,† Boston, Mass., Jonathan D. Ballon, Boston, Mass., Leopold Reiner, New York, N. Y., and David G. Freiman, Boston, Mass.*

Much of the confusion concerning the pathogenesis of pulmonary embolism stems from the lack of a reliable and physiologic method for its experimental production. A new approach, developed in this laboratory, has overcome many limitations inherent in previous technics.

The systemic infusion of heterologous canine serum induces, in dogs, a transient hypercoagulable state during which massive venous thrombosis develops in venous segments containing stagnant blood far removed from the site of infusion. This reaction occurs with extraordinary reproducibility without detectable vascular injury and without the introduction of foreign substances; the thrombus formed is invariably a single homogeneous red clot morphologically indistinguishable from a postmortem clot.

The fate of a single pulmonary embolus was investigated by inducing clots 4 cm. in length in both jugular veins and releasing 1 of these to the lung. In 20 such experiments pulmonary emboli, recovered minutes to hours after release, were

smaller than the control clots in the contralateral jugular vein and were frequently fragmented. In 14 "sham" experiments in which neither jugular vein clot was released and the animal sacrificed over a similar time span, the pulmonary arteries were found to be free of obstruction.

In 24 additional animals sacrificed 1 to 28 days after embolization, pulmonary emboli were always recovered up to the fourth day, were recovered in half of the animals sacrificed between the fifth and thirteenth day, but were never recovered between the fourteenth and twenty-eighth days. Clot adherence was noted only after the fifth day. In no animal was pulmonary infarction produced.

These unique experiments provide evidence that antemortem and postmortem clots can be morphologically indistinguishable and that pulmonary emboli can spontaneously fragment, lyse and finally disappear. Such findings, if valid for man, may clarify many discrepancies between clinical and pathologic observations in patients with pulmonary emboli.

Cardiac Effects of Methoxamine

James W. West, Santiago V. Guzman, Domingo M. Aviado, Jr., and Samuel Bellet, Philadelphia, Pa.

The direct cardiac effects of different vasopressor agents are of considerable clinical importance in judging their usefulness in various conditions. Most of the sympathomimetic amines in addition to their peripheral vasoconstrictor effect have a positive inotropic action on the heart.

The direct effects of methoxamine on the heart were studied in dogs anesthetized with morphine and pentobarbital sodium or a combination anesthesia (dial, urethane, pentobarbital). Catheterization of the circumflex or anterior descending branches of the left coronary artery via a carotid artery and cannulation of the coronary sinus via an external jugular vein were accomplished under fluoroscopic guidance. The data on coronary blood flow, myocardial contractility, cardiac output and electrocardiograms were obtained separately in 3 different series of experiments. Coronary blood flow was determined by collecting blood for a measured time from the coronary sinus cannula. Myocardial contractility was determined by a Walton strain gage sewed directly to the anterior surface of the left ventricle. Cardiac output was measured by the direct Fick method and cardiac electric activity by an electrocardiograph.

Methoxamine when given by intravenous injection (0.1 mg./Kg.) increased coronary blood flow, along with a rise in mean arterial blood pressure and a concomitant decrease in heart rate.

Intravenous infusion of 10 μg./Kg./min. of methoxamine decreased cardiac output and cardiac work, while total peripheral resistance increased.

Intracoronary arterial injections (0.001–0.4 mg./Kg.) either did not affect coronary blood flow or produced a very slight decrease. There was no immediate effect on blood pressure or heart rate. Myocardial contractility was not noticeably affected by small doses but with doses greater than 0.01 mg./Kg. depression of contractility occurred without immediate changes in the electrocardiographic pattern.

These experiments show that intracoronary arterial injections of methoxamine do not increase coronary blood flow, produce no direct positive inotropic effect on the myocardium but a negative inotropic effect occurs with large doses. Intravenous doses of the drug increased coronary blood flow, systemic arterial blood pressure and total peripheral resistance but decreased heart rate, cardiac output and cardiac work.

These experiments suggest that methoxamine has but a limited use in the therapy of hypotension caused by myocardial infarction because it manifests a potential cardiac depressing action and does not increase myocardial contractility.

Cardiac Effects of Intracoronary Arterial Injections of Nicotine

James W. West, Santiago V. Guzman, and Samuel Bellet, Philadelphia, Pa.

The direct cardiac effects of nicotine were studied in dogs anesthetized with pentobarbital sodium. Coronary arterial catheterization of the circumflex or anterior descending branch of the left coronary artery via 1 carotid artery and cannulation of the coronary sinus via 1 external jugular vein were accomplished with fluoroscopic guidance.

Intracoronary arterial injections of nicotine in doses of 0.25–0.5 μg./Kg. were given and measurements were made on coronary blood flow by timing the collection of a measured volume. Cardiac contractility was measured by means of a Walton strain gage sutured directly to the anterior surface of the left ventricle. Continuous electrocardiograms were taken using a precordial or epicardial lead.

Small doses of nicotine (approx. 0.05 μg./Kg.) produced a definite decrease in myocardial contractility but no other discernible effects. Larger doses of nicotine (approx. 0.25 μg./Kg.) increased coronary blood flow and myocardial contractility with no change in systemic blood pressure or heart rate. The electrocardiographic changes consisted of lowering or inversion of the T wave. These changes were qualitatively similar to the effects elicited by intracoronary injections of epinephrine and norepinephrine. All of these effects of nicotine produced by the larger dose were completely blocked by intracoronary injection of tetraethylammonium bromide (0.1 mg./Kg.). Still larger doses of nicotine (approx. 0.5 μg./Kg.) elicited the coronary chemoreflex (Bezold-Jarish) accompanied by a decrease in coronary blood flow. These effects were abolished

by bilateral vagotomy. In these experiments there was no evidence of coronary vasoconstriction resulting from nicotine injection. The results obtained in these experiments can best be explained by the presence in the heart of parasympathetic and sympathetic ganglia and chemoreceptors influenced by nicotine.

Complications Encountered in Patients With Primary Pulmonary Hypertension, Including the Management of Pregnancy

Ruth Whittemore, Maria F. Stack, Richard J. Waters, and Herbert S. Harned, Jr., New Haven, Conn.

The purpose of this paper is to present the results of studies in 5 patients with clinical evidence of primary pulmonary hypertension and a review of certain complications. Four of the patients were females from 12–21 years of age, the fifth patient being a 7-week old male infant.

Cardiac hemodynamic studies included the expected elevation of pulmonary arterial pressure, elevated right ventricular pressure and slight peripheral arterial unsaturation at the time of the studies. Pulmonary function studies were essentially normal as far as is known for this age group.

A comparison between these cases and those in the literature was made as to prognosis and complications. Problems encountered in 4 of the patients included brain abscess, rapidly progressive cardiomegaly at puberty and pregnancy. The infant of this series expired following angiocardiography, this procedure having been performed as a desperate measure. Postmortem examination confirmed the suspected clinical diagnosis. The hazards of certain diagnostic procedures in patients with this disease were stressed.

The management of pregnancy in 1 patient with consideration of the physiologic hemodynamic alterations, together with anticipated problems, were discussed. In addition, a compilation of the results was made of previously known pregnancies in patients with primary pulmonary hypertension.

A therapeutic trial of tolazoline hydrochloride was attempted in 3 of these patients with doubtful benefit. In addition, isopropylnorepinephrine was tried in 2 of the patients because of its vasodilatory effect and was considered ineffective for symptomatic relief.

This paper, then, presented 5 additional cases of primary pulmonary hypertension with the typical clinical features previously described and, in addition, various complications. A case that occurred very early in infancy, as well as a case managed during pregnancy, were included.

Range of the Normal Heart in Athletes: A Modernized Reanalysis

John W. Wilce, Columbus, Ohio.

A clinical study of the hearts of 237 personally known American athletes was presented to the 1941 meeting of the American Heart Association under the above title.

The objective of the study, now in its twenty-seventh year, was to obtain evidence as to the immediate, intermediate and eventual influence of athletic work stress as related to the human heart. Valid clinical guidance for activity is possible only through such evidence.

The then nonadequately, now established fact, of the enlargement of many American athletes' hearts by physical stress was examined. Enlargements were demonstrated in hearts which were not cases of organic heart disease. These hearts had experienced "predisposing factors to heart disease" with athletic stress superimposed. Seven cases were found with supposedly nonorganic enlargements with no history of "predisposing factors." These were postulated as so-called "athletic hearts," with unknown but postulated normal prognosis.

In 1941, only 12 predisposing factors to heart disease were accepted. Over 80 are now adequately proven. Reanalysis with modern knowledge and mortality facts reinterprets the 7 supposedly "strictly normal" but enlarged hearts, as other than "strictly normal."

The evidence suggests that there is no "athletic heart" in this sense. Many athletes with organic hearts are proven to compete in sports. Changes in heart size, increases and decreases, are demonstrated in organic hearts and "suborganic hearts" with "predisposing factors." Differing definitions of "normal" add confusing elements. The term suborganic (athletes) work heart is suggested, based on acceptance of the "adaptation syndrome" supported basically by the works of Starling, Eyster, and others. The positive literal interpretation of the term "athletic (strong, robust, vigorous, muscular) heart" is suggested for current clinical use. Objective standardization of the elements involved in total circulatory superiority and stress adaptation, awaits further basic investigation.

Serotonin, Antiserotonins, and Hypertension

Robert W. Wilkins and William Hollander, Boston, Mass.

Serotonins and antiserotonins have attracted considerable attention lately, especially because of their possible relation to the action of reserpine. Thus serotonin is said to be released by reserpine from its natural storage sites in the brain, the intestine, and the platelets. However, whether reserpine is an "antiserotonin" or a "serotonin activator" is still open to debate

A number of naturally occurring and synthetic chemical analogs of serotonin have been found to have antiserotonin effects. Of several such antiserotonins tried in this laboratory only 1, the benzyl analog of serotonin (BAS, Woolley), so far has appeared promising as a possible therapeutic agent in essential hypertension. Given intravenously (75 mg.), it blocks the pressor and hyperpneic effects of intravenous serotonin. Given orally (10–50 mg. 4 times a day) for several weeks to months it is a moderate hypotensive agent in about one third of hypertensive patients. Its side effects of sedation, increased intestinal motility, nasal stuffiness, and bradycardia resemble those of reserpine. However, whether its hypotensive effect in the dosage used for chronic oral administration is due to an "antiserotonin" action is still open to question. The evidence for and against this possibility and for and against a similar possibility for the clinical effect of oral reserpine in hypertensive patients will be presented, along with data on the clinical actions of BAS alone and in combination with reserpine and other hypotensive drugs.

Natural Course of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life. I. Prognosis with Special Reference to Survivorship

May G. Wilson and Wan Ngo Lim, New York, N. Y.

Basic data on the natural course of a chronic disease are essential for the evaluation of therapeutic procedures. The object of this study is to provide information on the natural course of rheumatic heart disease in the third, fourth and fifth decades of life. It is concerned with 757 out of 1,042 children under observation during the years 1916–1956 who reached the age of 20 or more years. The data presented should be useful in the selection of patients for cardiac surgery as well as for evaluation of the effect of surgical intervention on longevity. The major manifestations of rheumatic fever experienced by these patients from the onset of the disease will be related to the degree of residual cardiac damage. Prognosis also will be considered in terms of age, sex, type of valvular lesion and degree of cardiac chamber enlargement.

A comparison of the major manifestations of rheumatic fever experienced, and degree of residual cardiac damage sustained revealed a close correlation with the incidence of active carditis, acute and subacute. Increased cardiac damage in the absence of a recurrent carditis was not observed with the passage of time. The over-all average annual mortality rate for the ages 20–52 years was one-half that previously observed in the first 2 decades of life. There was no significant sex difference in survivorship. Survivorship for 392 patients with mitral insufficiency and moderate enlargement of the heart followed closely that of the general population while it was significantly lower for 269 patients with mitral stenosis and insufficiency. The lowest survivorship was found among 96 patients with combined aortic and mitral lesions. A comparison of survivorship for patients with moderate and marked cardiac enlargement showed a significant decrease in longevity for those with markedly enlarged hearts.

Prognosis is primarily determined by the extent of cardiac damage sustained in the first 2 decades of life.

Studies of Two Pure Veratrum Alkaloids, Protoveratrine A and Protoveratrine B

Bertram M. Winer, Boston, Mass.

The pharmacologic differences between protoveratrine A and protoveratrine B, substances which differ chemically by a single hydroxy group, have been reported to be small and of little clinical significance. However, we have observed marked differences in the activity of these agents in a controlled study of dose-responses in 16 patients with sustained hypertension.

Orally, protoveratrine A in doses of 0.4 to 1.4 mg. was a potent hypotensive agent with a narrow range between hypotensive and emetic doses. Protoveratrine B in oral doses of less than 4 mg. did not affect the blood pressure. However, 8 patients given total daily doses of 10–25 mg. of this agent had significant decreases in blood pressure without vomiting. Normotension persisted as long as 18 hours after discontinuation of the drug.

Muscular symptoms resembling myotonia, an unusual side-effect, have been reproducibly induced by large oral doses of protoveratrine B. This is consistent with the known ability of veratrum alkaloids to render nerve and skeletal muscle capable of responding to brief stimuli in a prolonged manner.

Preliminary studies after intravenous administration suggest that protoveratrine B has a wider dosage range between hypotensive and emetic effects than protoveratrine A. Data from 41 experiments in 3 patients indicate that the alkaloids have hypotensive activity at nearly equal doses, but that emetic activity occurs at a lower dosage of protoveratrine A than protoveratrine B. The dosage range for A averaged 1.6 to 2.4, for B 1.7 to 3.4 μg./Kg.

Electrocardiographic studies have shown that both alkaloids can reverse the pattern of left ventricular strain, slow the sinoauricular rate, induce ectopic ventricular activity or initiate T wave inversion in the left precordial leads. The latter 3 effects are reversible by atropine.

These observations have therapeutic significance and provide definite evidence of the value of the use of single pure alkaloids rather than mixtures.

Further Emphasis on the Role of the Vascular System in the Production of the Ballistocardiographic Pattern Due to the Heart Beat

Nahum J. Winer, New York, N. Y.

This report attempts to emphasize and integrate observations using the head-foot dimensional direct body ballistocardiograph in one or more of displacement, velocity and acceleration aiming to further validate its clinical practicability.

Functional pattern abnormality, in otherwise normal individuals, is reflected in the neurasthenic or flaccid abdomen in which suspended mid-inspiration promptly corrects, in amplitude and configuration, both resting abnormality and abnormality following exercise. Exercise may also improve such resting abnormality. Similarly deterioration following nitroglycerin is corrected in mid-inspiration except for HIJ which may remain bifid. Functional abnormality is attributed to "splanchnic pooling" which, following nitroglycerin, may proceed to severe hypotension or syncope and is counteracted by suspended mid-inspiration comparable to the abdominal binder.

Organic pattern abnormality is exemplified by a young adult with angina of impending infarction and sudden death presenting serial ballistic deterioration despite normal resting electrocardiograms. This was not counteracted by suspended mid-inspiration. Also, exercise further deteriorated the abnormality.

Other, more pathologic, functional abnormality is reflected in the anginoid diastolic hypertensive-systolic normotensive individual presenting electrocardiographic, exercise induced, insufficiency and ballistic, even resting, abnormality. Antipressor-vasodilator drugs (e.g., rauwolfia with pentaerythroltetranitrate) improve both.

Tobacco smoking produced deterioration despite partial denicotinization and filters. This was not completely counteracted, if at all, by suspended mid-inspiration and was improved by alcohol, nitroglycerin and "neurovascular blocking" (combined dihydroergocornine, dihydroergocristin, dihydroergokryptin). In pectus excavatum, suspended mid-inspiration produced progressive transitional deterioration. Overall smoking deterioration is attributed to combined reduction in available blood to the heart by vascular constriction and "exhaustion" of the "pulmonic pool" rendered visible in pectus by mechanically reduced pulmonic capacity.

Diastolic amplitude (L wave) is offered in differential between patent ductus and intra-aortic septal defect—doubtful even with catheterization. It is elevated in the former by downward diastolic thrust; depressed in the latter by upward diastolic thrust.

Controlled Study of Three Methods of Prophylaxis Against Streptococcal Infection in a Population of Rheumatic Children. I. Streptococcal Infections and Recurrences of Acute Rheumatic Fever in the First Two Years of the Study

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Two years of a carefully controlled 5-year study of 400 children with unequivocal histories of rheumatic fever to determine the incidence of streptococcal infection and rheumatic recurrences in 3 randomly selected comparable prophylaxis groups have been completed. In addition to obtaining reliable information as to the relative effectiveness of the 3 prophylactic regimens, the natural history of rheumatic fever and rheumatic heart disease in the proven absence of recurrent streptococcal infections is being studied.

The 3 prophylactic regimens under study are: (1) Sulfadiazine, 1.0 Gm./day by mouth in a single dose, (2) penicillin, 200,000 units a day by mouth in a single dose, ½ hour before breakfast, (3) benzathine penicillin, 1.2 million units in 2 ml. by monthly intramuscular injection.

Throat cultures were taken on every patient at each monthly visit, and all β-hemolytic streptococci were grouped with an antiserum to the group A streptococcus. Antistreptolysin O determinations were done on each bleeding from every patient. These bleedings were taken bi-monthly and whenever an elevation was found in the routine antistreptolysin O, a serial determination of antistreptolysin O, of antistreptokinase and of antihyaluronidase was carried out.

A total of 95 streptococcal infections occurred in 87 patients during the first 2 years of the study, 40 during the first year and 55 during the second. There were 310 patients in the study at the end of the first year and 384 at the end of the second. The 2 study years were comprised of 6,812 patient months. The over-all infection rate for the 2 years was 1.4/100 patient months.

The numerical distribution of the streptococcal infections among the 3 prophylactic groups was: benzathine penicillin 15, penicillin 36, sulfadiazine 44.

A total of 13 recurrences of acute rheumatic fever occurred during the 2 years, 2 of the patients having chorea only following proven streptococcal infections. These 13 recurrences represented 15 per cent of the 87 children who had 1 or more streptococcal infections. The rheumatic recurrence rate for the entire group studied was 0.19 per 100 patient months. Nine of the patients, including the 2 with pure chorea were on oral penicillin, 4 were on

sulfadiazine and none were on dibenzylethylenediamine penicillin G.

Peripheral Venous and Arteriolar Responses to Moderate Reductions in Effectively Circulating Blood Volume in Man

J. Edwin Wood and John W. Eckstein, Boston, Mass.

This study was undertaken to assess forearm venous and arteriolar responses to venous pooling in the legs.

Normal subjects were studied in a tilted (30° head-up) position. Venous pooling was prevented with pneumatic counterpressure leggings during control periods. Leg congestion was produced by deflation of the leggings and inflation of a cuff high on each thigh. Forearm venous distensibility was measured plethysmographically from the increase in volume due to a rise in local effective venous pressure of 1 to 31 mm. Hg, produced with a proximal congesting cuff. An increase in venous distensibility indicated venodilatation; a decrease, venoconstriction. Blood flow was calculated from the initial rate of forearm volume increase. Venous pressure was measured continuously in the opposite forearm proximal to an arterial occluding wrist cuff.

Venoconstriction occurred in response to leg congestion in 20 of 21 tests on 10 subjects. Venous distensibility averaged 3.1 ml./100 ml. forearm tissue in the control period, and 2.5 ml./100 ml. after leg congestion. Blood flow was measured in these 20 tests. After leg congestion arteriolar constriction occurred prior to venoconstriction in 13; venoconstriction occurred first in 1. Arteriolar constriction was present throughout each of the 6 remaining experiments. Leg counterpressure reapplication in 17 experiments resulted in venodilatation in every case, followed by arteriolar dilatation in 12; arteriolar constriction persisted in 5.

Venous pressure was measured in 9 tests and always decreased prior to venoconstriction with leg congestion. In 7 tests, after leg counterpressure reapplication, brief persistence of venoconstriction with an associated venous pressure overshoot (7–24 mm. water) was observed.

Leg congestion in the head-up position usually results in immediate arteriolar constriction and venous pressure decline followed by venoconstriction. Blood volume restoration usually causes in sequence venous pressure overshoot, venodilatation and arteriolar dilatation.

Evaluation of an Indicator-Dilution Method for Quantitation of Mitral Insufficiency

Edward Woodward, Jr., H. J. C. Swan, Samuel J. Kuykendall, F. Henry Ellis, Jr., and Earl H. Wood, Rochester, Minn.

Detection of indicator in the left atrium (LA) immediately following its injection into the left ventricle (LV) is proof of retrograde passage through the mitral valve.

If cardiac output is constant during successive injections of equal doses of dye into LV and LA and if there is uniform mixing of dye regurgitated through the mitral valve with LA blood following LV injection, and of dye with LA blood following LA injection, then the proportion of dye regurgitated into LA (R_i) is related to the ratio of the areas of the curves recorded from the left atrium, that is, $R_i = (\bar{c} \cdot T_p)_{LV} / (\bar{c} \cdot T_p)_{LA}$, in which $\bar{c}$ is mean concentration and T_p is passage time of LA curves following LV and LA injections respectively.

Dilution curves were recorded simultaneously at the LA and femoral artery following successive injections of T-1824 into LA, LV and pulmonary artery of 7 dogs before and after acute mitral insufficiency (MI) was created and of 4 with chronic mitral insufficiency. The average calculated proportion of regurgitated dye (R_i) was 2 (0–10) per cent respectively in the 7 normal dogs, and ranged from 27–53 per cent in acute MI and from 38–87 per cent in chronic MI.

Left atrial and radial-artery dilution curves were recorded similarly in 16 patients during combined right and left heart and aortic catheterization. Calculated R_i in 4 with no MI detectable subsequently by gloved finger at operation was 0–25 per cent, in 2 with grade 1 MI it was 0–34 per cent, and in 2 with grade 3 MI it was 0–42 per cent.

Occasional large differences in contour and area of LA curves following LA and pulmonary-artery injections indicated incomplete mixing of dye in LA. This, along with variations in injection site, are sources of error in the method.

Transformation of the Aortic Pulse Contour in Man

J. Leo Wright and Earl H. Wood, Rochester, Minn.

Photokymographically recorded arterial pressure pulses (paper speed: 150 mm./sec.) obtained simultaneously from (1) the aortic arch (via arterial catheter-strain gage manometer system), (2) the radial artery, and (3) the femoral artery (via indwelling needle-strain gage manometer systems) were compared in 10 normal persons, 20 patients with aortic stenosis, 5 patients with aortic insufficiency and 5 patients with coarctation of the aorta (brachial-artery catheterization).

Graduated withdrawal of the arterial catheter permitted study of the transformation of the aortic contour over 5 cm. segments of aortic-radial and aortic-femoral systems.

Instead of 1, the systolic portion of the central arterial pressure pulse appears to consist of 2 main waves: (1) an initial wave which comprises the first portion of the contour extending from the onset of the pulse to the anacrotic pause, and (2) a secondary wave which reflects sudden changes in stroke output,

such as extrasystoles, atrial fibrillation, Valsalva maneuver.

In normal persons, the secondary wave is the systolic maximum of the aortic pressure pulse, but as the pulse wave travels peripherally in the aortic-radial system, amplification of the initial wave occurs, and at the radial artery it comprises the systolic peak; the secondary wave appears on the radial pulse contour between the peak and the dicrotic pause.

In aortic stenosis there is little change in the relationship of the initial and secondary waves of the aortic contour as the pulse wave moves peripherally and, unlike the normal, the secondary wave commonly is the systolic maximum of the radial contour.

In aortic insufficiency and coarctation, the transformation of the aortic contour in the aortic-radial system tends to resemble the normal, but quantitatively the magnitude of the initial and secondary waves characteristically varies from the normal.

Clinical Significance of Serum Enzyme Alterations Associated With Myocardial Infarction

Felix Wroblewski and John S. LaDue, New York, N. Y.

Acute myocardial infarction is associated with increases in the activity of serum glutamic oxaloacetic transaminase (SGO-T) and serum lactic dehydrogenase (SLD). Other cardiac tissue enzymes present in great enough concentrations in human heart muscle may be expected to be released into the circulation following acute myocardial infarctions. Serum transaminase and lactic dehydrogenase activities can be measured in any clinical laboratory by chromatographic, spectrophotometric, and colorimetric technics. SGO-T and SLD activity increases 2 to 10 times normal within 6 to 12 hours post-infarction with the peak elevations at 24 to 48 hours. SGO-T rises somewhat more rapidly than SLD. The peak rise of serum enzyme activity is roughly proportional to the extent of myocardial tissue damage. The mechanism of increase in the enzyme activity is thought to be due to the release of enzyme into the serum from infarcted heart muscle which has 5,000 to 10,000 times the enzyme activity of serum.

The SGO-T and SLD changes not only permit confirmation of the clinical and electrocardiographic diagnosis of myocardial infarction but also reflect semiquantitatively the amount of cardiac tissue injury. In the presence of equivocal electrocardiographic changes or when the classical patterns of myocardial infarctions are obscured by bundle-branch block, aberrant conduction, reflection of evolving or healed infarction, or involvement of so-called "silent" areas the serum enzyme changes assist in making a definitive diagnosis of acute myocardial infarction. Pulmonary infarction, pericarditis and left and right heart strain are not associated with significant serum enzyme changes above the normal range. Differential diagnosis of these states from myocardial infarction is facilitated by following the serial and quantitative alteration in serum enzymes during the acute clinical phase in patients with chest pain which may be due to acute myocardial infarction.

The serum enzymes are altered in several other specific clinical settings but the serial changes are qualitatively and quantitatively different than those observed following acute myocardial infarction.

Although the size of infarction does not necessarily correlate with prognosis, it has been observed that a myocardial infarct associated with a peak rise in serum glutamic oxaloacetic transaminase greater than 300 units carries an ominous prognosis in terms of survival.

Ventricular Septal Defects in the Infant Age Group

Stella C. Zacharioudakis, Kornel Terplan, and Edward C. Lambert, Buffalo, N. Y.

An isolated ventricular septal defect is now becoming recognized to be a relatively common cause of heart failure and death during infancy.

This defect comprised 23 (8 per cent) of the 288 major cardiac malformations observed at autopsy over a 20-year period at the Children's Hospital of Buffalo. The only anomaly exceeding it in frequency was that of complete transposition of the great vessels. The age at death in 20 out of the 23 cases was less than 6 months. The oldest patient in the series was 16 months. This high fatality rate in early infancy emphasizes the need for early diagnosis and surgery.

The cardinal clinical and postmortem features in the 23 cases were: (1) Evidence of both right- and left-sided heart failure and moderate to marked cardiac enlargement in all; (2) the presence of a loud systolic murmur along the lower left sternal border usually with an accentuated pulmonic second sound; (3) cyanosis, present only intermittently or terminally; (4) variability of electrocardiographic findings which were available in 15 cases (in 7 of these there was evidence of combined ventricular hypertrophy, in 5 right, and in 2 left ventricular hypertrophy); and (5) variation in size of the defects between 3 and 17 mm. in diameter. There was no consistent correlation between the size of the defect and the clinical manifestations and course of illness.

Heart catheterization data are presented from 6 of these cases. In all there was evidence of a large left-to-right shunt at the level of the right ventricle and marked right ventricular and pulmonary artery hypertension. In 5 of these infants this pressure was essentially the same as the systolic pressure measured in a systemic artery. In 3 of the patients there was,

in addition, evidence of a left-to-right shunt at the level of the right atrium. In 2, the catheter was directed from the right ventricle into the aorta.

Histologic data available in 5 of the 6 catheterized patients showed varying degrees of thickening of the media in small and mid-caliber branches of the pulmonary arteries.

Burger Triangle: A Summary of Experience

Zang Z. Zao, Milton R. Hejtmancik, and George R. Herrmann, Galveston, Tex.

This paper, it is hoped, will be a short "bridge" leading us physicians from physically not founded Einthoven triangle to physically founded Burger triangle.

The Burger triangle was explained with simple mathematics. Its various shapes were correlated to the Einthoven triangle as a quantitative measure of the inaccuracy of the latter. The use of this criteria on the influence of heart vector eccentricity and length on the inaccuracy of the Einthoven triangle was made from a RLF plane electrolytic model. Burger triangles were constructed directly from living toad hearts in situ. QRS and T triangles from the same toads were almost identical, which indicates that the hypothesis that QRS and T vectors from same subjects differ in length and occupy different heart regions, could not be confirmed experimentally, at least not on toads. The simplification of the use of Burger triangle was illustrated.

Two diagrams were described in detail for clinical use. These supply easily comparable results from Einthoven triangle and "normal" Burger triangle. Thus the Einthoven inaccuracy may be checked each time without further effort. Diagrams may also be used to convert Einthoven data into Burger data at a glance. The Burger triangle of other shapes (e.g., in bundle-branch block, premature beats) may be added into diagram B in curve form.

Different Vectorcardiographic Forms Taken with Wilson Tetrahedron and with the Same Electrode Places after Applying Burger Coefficients

Zang Z. Zao, Milton R. Hejtmancik, and George R. Herrmann, Galveston, Tex.

The Wilson tetrahedron often gives too small x (transverse) component of the heart vector so that its particulars are difficult to estimate, especially in the transverse plane. The physically founded Burger coefficients make a linear transformation of the vectorcardiographic forms whereas local peculiarities remain. Such a transformation is extremely important for clinical vectorcardiographic comparison. In practice the latter method can be made just as simple as the former.

A Plea for Open Cardiac Surgery

Henry A. Zimmerman, Cleveland, Ohio.

The first 24 cases of open cardiac surgery for a number of different congenital lesions have emphasis and impressed us so that we adhere to the principle that all intracardiac work must in the future, by necessity, be done with an open technic for proper repair and evaluation.

Though our team has had considerable experience with closed methods, we have been at times very much upset with the results of such closed technics.

In a series of 6 ventricular septal defects, the septal defects were multiple; in 1 case there were 3 distinct septal defects in the ventricular septum and these were closed.

These defects we feel are not best closed by a method of stopping the heart with potassium as one cannot substantiate the degree of repair as well as if the heart is beating.

Two cases of transposition of the great vessels were corrected. One patient died 4 hours postoperatively and 1, 18 hours postoperatively.

Six cases of pulmonary stenosis were found with an accompanying intraventricular septal defect or significant degrees of infundibular stenosis which were not detected prior to the time of surgery.

Use of the Image Amplifier for Differential Angiocardiograms in Congenital Heart Disease

Henry A. Zimmerman, Cleveland, Ohio.

During the last 2 years we have used the image amplifier to carry out angiocardiograms and selective angiocardiograms in cases of congenital heart disease with a variety of defects.

A Lemon arterial catheter is used to inject the dye, 70 per cent Diodrast into selected areas of the heart for study and a 16 mm. motion picture at 16 frames/sec. is taken as the dye courses through the heart.

This procedure markedly lowers the radiation dose to the patient as well as using small doses of the contrast media which allows for multiple injections.

Slides will be shown from a time and motion study of cases of intra-atrial, pulmonic stenosis, intraventricular and transposition of the great vessels to emphasize the use of this technic for the diagnosis of congenital cardiac lesions.

Effects of External Electric Currents on Cardiac Arrhythmias

Paul M. Zoll, Arthur J. Linenthal, Leona R. Norman, Milton H. Paul, and William Gibson, Boston, Mass.*

The direct application of stimulating or countershock current to the exposed heart has long been known to produce atrial or ventricular beats or to terminate ventricular fibrillation. These technics of

stimulation and defibrillation have been limited in clinical use because of the necessity of opening the chest. Now, however, we have developed technics whereby these currents are applied externally to arouse the heart from ventricular standstill, to stop ventricular fibrillation, and to terminate other rapid arrhythmias.

Single or repetitive electric stimuli applied directly to the heart are known to produce single ectopic beats or to assume control of cardiac rhythm. Electric stimulation applied externally across the unopened chest acts like an intrinsic cardiac pacemaker. This technic of producing effective cardiac beats constitutes a valuable means of cardiac resuscitation from cardiac arrest as it occurs in Stokes-Adams disease, reflex vagal stimulation, drug-induced standstill, and unexpected circulatory arrest during anesthesia.

Electric countershock across the exposed heart has become the accepted therapy for ventricular fibrillation. In the experimental animal we have found that countershock current applied across the unopened chest instantaneously terminates atrial fibrillation and atrial, nodal, and ventricular tachycardia, as well as ventricular fibrillation.

This technic of external countershock has been applied in 5 patients to terminate ventricular fibrillation 12 times and ventricular tachycardia 1 time. On 3 occasions in 1 patient countershock stopped ventricular fibrillation but was followed by ventricular standstill; spontaneous ventricular rhythm returned after short periods of external electric stimulation. He survived and recovered completely.

Arousal from ventricular standstill and termination of atrial fibrillation, supraventricular and ventricular tachycardia, and ventricular fibrillation by these 2 external technics have wide clinical potentialities. Outside the operating room and in seriously ill patients in whom thoracotomy and cardiac massage are particularly inadvisable, external stimulation or countershock may offer the only effective therapy.

Relation of Bacterial Endotoxins to Shock Syndrome

Benjamin W. Zweifach† and Lewis Thomas, New York, N. Y.

The similarity between various aspects of the shock syndrome and the effects produced by bacterial endotoxins is so striking as to be highly suggestive of an etiologic relationship. The concept is especially provocative in view of the parallel courses of the development of trauma resistance and the adaptation or tolerance to bacterial endotoxins, and the studies of Fine and co-workers relating the irreversible aspects of hemorrhagic shock to the breakdown of bacterial defense mechanisms.

Several categories of study were conducted in rats and rabbits to test the validity of this hypothesis: (1) Lipopolysaccharide extracts of gram negative bacteria were administered prior, during and subsequent to hemorrhagic and traumatic shock; (2) endotoxin-tolerant animals were evaluated with respect to their capacity to withstand shock; (3) trauma-resistant animals were challenged with bacterial endotoxins; (4) agencies such as cortisone and RES blockade, known to predispose to bacterial endotoxins, were studied in relation to the shock syndrome in both normal and trauma-resistant animals.

The parameters used in addition to survival included blood leucocyte changes, microscopic observations of the circulation in the mesentery, blood transaminase levels, and carbon clearance as a measure of RES activity.

The findings in general indicate that: 1. *E. coli* extracts (Lane's or Westphal's) increased the susceptibility of normal rats to drum trauma and hemorrhagic shock. 2. Rats made tolerant to bacterial endotoxins became more resistant to drum shock and hemorrhage when low doses (50–100 μg.) of the lipopolysaccharide extracts are used. 3. Trauma-resistant rats showed no increased tolerance to the lethal effects of large doses of endotoxin (2–4 mg. i.p.). 4. Blockade of the RES made both normal and trauma-resistant animals highly susceptible to shock.

Although the data are highly suggestive of a relationship between endotoxins and shock, the possibility exists that the syndrome is associated with a generalized disturbance in some basic homeostatic system, such as the reticuloendothelial system, of which the reaction to endotoxins represents but 1 of the contributing factors.

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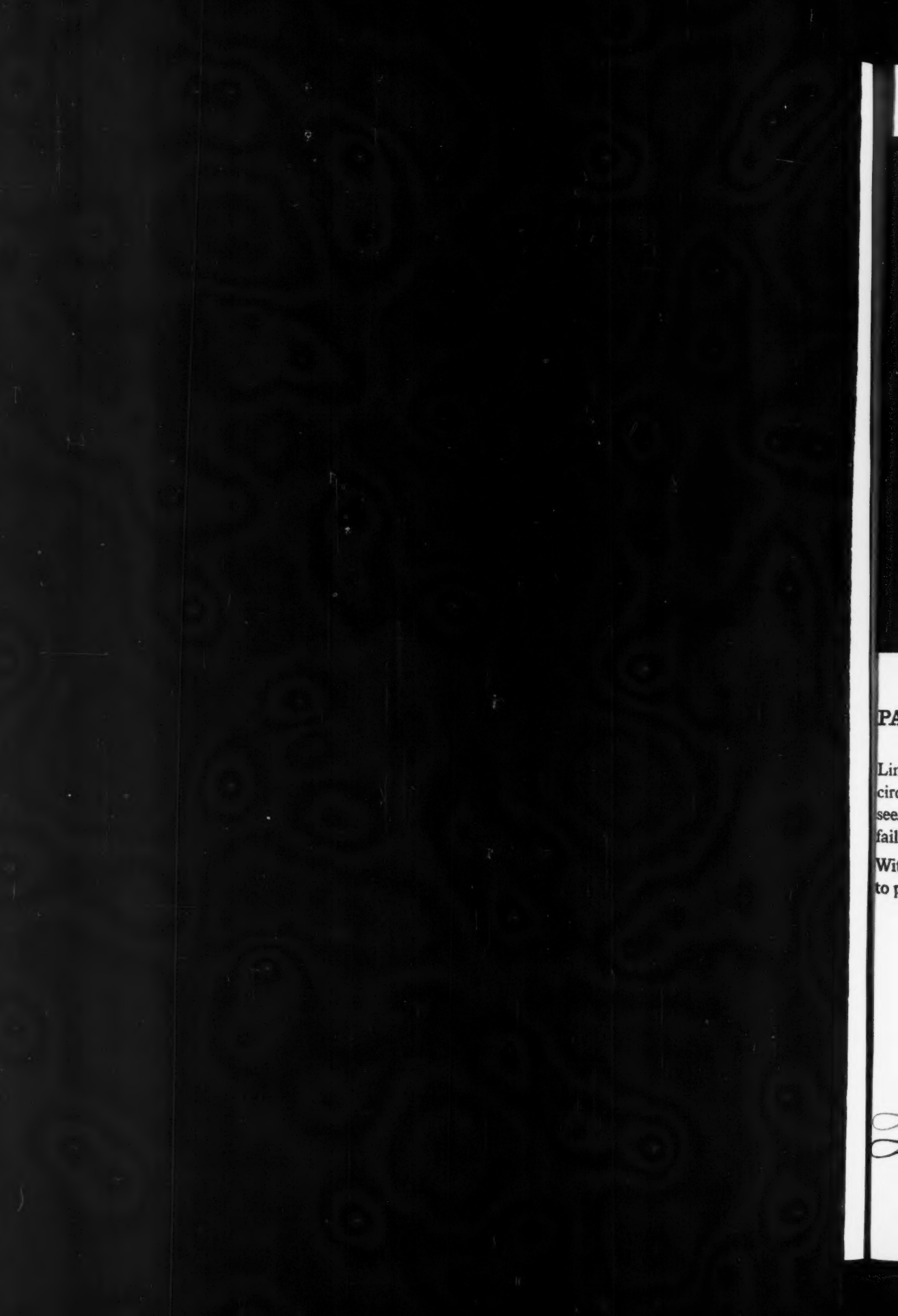

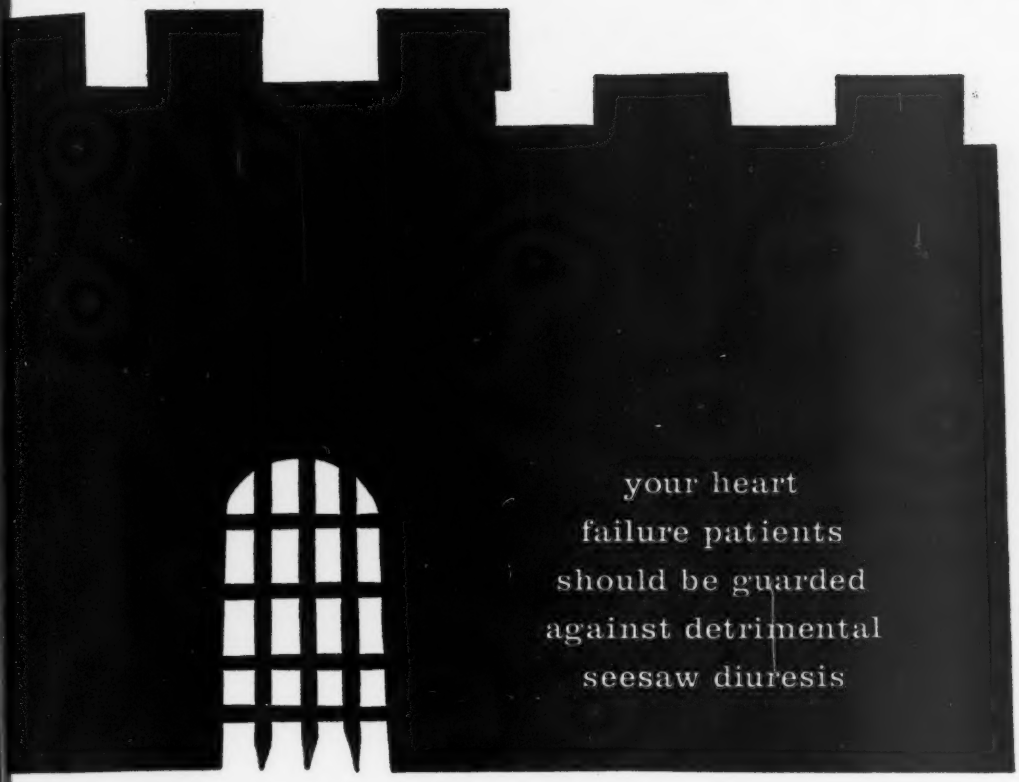

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